UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

DEPOMED, INC, Plaintiff(s), v. ACTAVIS ELIZABETH LLC, et al. Defendant(s).	***REDACTED*** Civil Action No. 12-1358 (JAP) **OPINION** ~~----**FILED UNDER--~~ ~~---TEMPORARY SEAL**~~ ~~----(pending motion to seal)--~~

PISANO, District Judge.

This is a Hatch-Waxman patent infringement action brought by Plaintiff Depomed, Inc. ("Plaintiff" or "Depomed") against defendants, Actavis Elizabeth LLC and Actavis Inc. (together, "Defendant" or "Actavis") in connection with Defendant's filing of an Abbreviated New Drug Application ("ANDA") seeking approval to sell generic gabapentin once-daily tablets. A bench trial was held May 12, 2014 to May 20, 2014, and the parties presented evidence on the questions of whether Defendant infringes any of the asserted claims in the seven patents-in-suit and whether the asserted claims are obvious and/or indefinite. This Opinion constitutes the Court's findings of fact and conclusions of law. As set forth below, the Court finds that Plaintiff has shown by the preponderance of the evidence that Defendant infringes the asserted claims, and further finds that Defendants have not shown by clear and convincing evidence that the asserted claims are invalid.

A. THE PARTIES

Plaintiff Depomed Inc. is a corporation organized under the laws of California, with a principal place of business in Newark, CA. Final Pretrial Order ("FPO"), Stipulated Facts ("Stip. Facts") ¶1. Depomed, a specialty pharmaceutical company, is the holder of New Drug Application ("NDA") No. 22-544, by which the United States Food and Drug Administration ("FDA") granted approval for tablets containing the active ingredient 1-(aminomethyl) cyclohexaneacetic acid (known as "gabapentin"). *Id*. ¶ 2; Tr.[1] 373:8. These gabapentin tablets are sold by Depomed in the United States under the brand name Gralise in dosage sizes of 300 mg and 600 mg. Stip. Facts. ¶ 3. Gralise was approved by the FDA for treatment of post-herpetic neuralgia ("PHN"). *Id.* ¶ 106. Presently, Gralise is the only once-a-day gabapentin product indicated for PHN available in the marketplace that is approved for commercial sale by FDA. *Id.* ¶ 107. Depomed began selling Gralise in or about October of 2011. *Id*. ¶ 108.

Defendant Actavis LLC is a limited liability corporation organized and existing under the laws of the State of Delaware, having a place of business in Morristown, New Jersey. *Id*. ¶ 4. Defendant Actavis Elizabeth LLC is a limited liability company that is wholly owned by Actavis LLC. *Id*. ¶ 5. Actavis Elizabeth LLC is organized and exists under the laws of the State of State of Delaware, having a principal place of business in Elizabeth, New Jersey. *Id*. On October 31, 2011, Defendant submitted ANDA No. 203611 with the FDA seeking approval to market generic gabapentin extended-release oral tablets in dosage strengths of 300 mg and 600 mg (the "ANDA product") prior to the expiration of the patents-in-suit. *Id.* ¶ 14.

[1] "Tr." Refers to the transcript of the May 14-20, 2014 bench trial.

B. NATURE OF THE ACTION

The present action is for patent infringement under 35 U.S.C. § 271(e)(2)(A), 271(a), (b), and (c) and under the Hatch-Waxman Act, codified in part at 21 U.S.C. § 355(j). Defendant has counterclaimed for a declaration that it does not and will not infringe any valid claim of the patents-in-suit, and for a declaration that patents-in-suit are invalid.

C. THE PATENTS-IN-SUIT

As set forth below, Depomed asserts against Actavis a number of composition and method claims. These claims are directed to a type of extended-release gabapentin oral dosage form that releases gabapentin in the stomach over several hours and delivers the drug in such a way that an individual achieves certain blood concentrations of the drug and that the drug has a therapeutic effect:

1. Platform/Gastric Retention Patent

a. U.S. Patent No. 6,635,280

United States Patent No. 6,635,280 (the "'280 Patent"), entitled "Extending the Duration of Drug Release Within the Stomach During the Fed Mode," issued on October 21, 2003, to Depomed from a patent application filed on November 6, 2001, as a continuation from United States Patent No. 6,340,475 ("the '475 Patent"). Stip. Facts ¶¶ 8, 50. FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the "Orange Book") identifies the expiration date of the '280 Patent as September 19, 2016. *Id.* at ¶ 8.

Depomed has asserted claims 1, 12, 14 and 45 of the '280 Patent in this case.[2] Stip. Facts ¶ 51.

Claim 1 of the '280 Patent is directed to:

> A controlled release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 15:85 to 80:20, said dosage form being one that when swollen in a dimensionally unrestricted manner as a result of imbibition of water is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode, that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid, that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug after such immersion, and that remains substantially intact until substantially all of said drug is released.

Stip. Facts¶ 53, '280 Patent (JTX 2) at col. 17, ll. 45-61. Claims 12, 14, and 45 depend from claim 1. Claim 12 adds the limitation that the "polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 5,000,000 to about 8,000,000." Stip. Facts. ¶ 59. Claim 14 adds the limitation that the "polymeric matrix upon immersion in gastric fluid retains at least about 60% of said drug one hour after such immersion." *Id*. at ¶ 60. Claim 45 adds the limitation that the "dosage form releases substantially all of said drug within about ten hours after immersion in gastric fluid." *Id.* at ¶ 61.

[2] With one exception noted *infra*, each of the patents-in-suit are being asserted against both dosage forms in the ANDA, *i.e.*, the 300mg and 600mg tablets.

2. Oval/Gastric Retention Patent

a. U.S. Patent No. 6,488,962

United States Patent No. 6,488,962 (the "'962 Patent"), entitled "Tablet Shapes To Enhance Gastric Retention of Swellable Controlled-Release Oral Dosage Forms", issued to Depomed as assignee of the inventors on December 3, 2002, from a patent application filed on June 20, 2000. Stip. Facts ¶¶ 7, 40. The Orange Book identifies the expiration date of the '962 Patent as June 20, 2020. *Id.* ¶ 7. Plaintiff's product Gralise is an embodiment of the asserted claims of the '962 Patent. *Id.* ¶ 111.

None of the four asserted claims from this patent have been asserted against Defendant's 300 mg dosage form; claims 5, 8, 10, and 13, from the '962 Patent are being asserted against the 600 mg tablet only. Claims 5, 8, and 10 are dependent upon claim 1. Claim 13 depends from Claim 10.

Independent claim 1 of the '962 patent reads as follows:

> A controlled-release oral drug dosage form for releasing a drug into at least a portion of a region defined by the stomach and the upper gastrointestinal tract, said dosage form consisting essentially of a solid monolithic matrix with said drug contained therein, said matrix being non-circular in shape and having first and second orthogonal axes of unequal length, said matrix being one that swells in an unrestricted manner along both such axes upon imbibition of water, the longer such axis having a maximum length of 3.0 cm when said matrix is unswollen, and the shorter such axis achieving a minimum length of 1.2 cm within one hour of immersion of said dosage form in water and wherein said matrix has a shape which when projected onto a plane, is either an oval or a parallelogram.

JTX 1 at col. 11, ll. 14-26, Stip. Facts ¶ 43. Claims 5, 8, and 10 add the following limitations, respectively: (i) the dosage form where the "shorter axis has a length of 0.7 cm to 1.5 cm when said matrix is unswollen"; (ii) the dosage form where the "longer axis has a maximum length of 2.5 cm when said matrix is unswollen"; and (iii) where the "matrix is a

water-swellable polymer". JTX 1 at col. 11, ll. 38-39, 47-48 and 53-54; Stip. Facts¶¶ 42, 46-48. Claim 13 depends from claim 10, and adds the following limitation: the dosage form where the "water-swellable polymer is a member selected from the group consisting of poly(ethylene oxide), hydroxypropylmethyl cellulose, and hydroxyethyl cellulose". JTX 1 at col. 12, ll. 2-5; Stip. Facts ¶¶ 42, 49.

3. The Gabapentin Patents[3]

a. U.S. Patent No. 7,438,927

United States Patent No. 7,438,927 (the "'927 Patent"), entitled "Methods of Treatment Using a Gastric Retained Gabapentin Dosage," issued to Depomed on October 21, 2008, from a patent application filed on October 25, 2002. Stip. Facts ¶¶ 9, 62. The Orange Book identifies the expiration date of the '927 patent as February 26, 2024. *Id.* ¶ 9. The use of Gralise in treating post-herpetic neuralgia ("PHN") embodies the asserted claims of the '927 Patent. *Id.* at ¶ 112.

Depomed has asserted claims 18, 25, 26, 34, 61 and 62 of the '927 Patent in this action. *Id.* ¶ 63. Each of the asserted claims depend from either of two independent claims – claim 17 (claims 18, 25, 26, 61) or claim 33 (claims 26, 62). Neither claim 17 or 33 is asserted in this litigation.

Claim 17 of the '927 Patent is directed to:

> A method of treating neuropathic pain in a mammal comprising administering a therapeutically effective amount of a daily dosage of about 100 mg to about 4800 mg of gabapentin or a pharmaceutically acceptable salt thereof, dispersed in a gastric retained dosage form to the mammal in which a fed mode has been induced, wherein the dosage form comprises a single polymer matrix comprising at least one swellable hydrophilic polymer

[3] U.S. Patents No. 7,438,927, No. 7,731,989, No. 8,192,756, No. 8,252,332 and No. 8,333,992 are herein referred to collectively as the "Gabapentin Patents."

> that swells in a dimensionally unrestrained manner by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach of the mammal, and wherein upon contact with water, gabapentin is released by diffusion from the dosage form over a period of at least five hours and at least 40 wt% of the gabapentin is retained in the dosage form one hour after administration.

JTX 3 at col. 12, ll. 38-51; Stip. Facts¶ 65.

Asserted claims 18, 25, 26, and 61 depend from claim 17 and, respectively, add the following limitations: (i) the dosage form is administered once daily; (ii) the gastric retained dosage form releases gabapentin to the stomach, duodenum and small intestine; (iii) dosage form provides administration of at least 85 wt % of the gabapentin to be delivered over a period of about 5-12 hours; and (iv) the mammal is a human.

Claim 33 of the '927 Patent reads as follows:

> A method of administering a therapeutically effective amount of a daily dosage of about 100 mg to about 4800 mg of gabapentin to a mammal, comprising administering gabapentin or a pharmaceutically acceptable salt thereof, dispersed in a gastric retained dosage form to the mammal in which a fed mode has been induced, and wherein the dosage form comprises a single polymer matrix comprising at least one swellable hydrophilic polymer that swells in a dimensionally unrestrained manner by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach of the mammal, and wherein upon contact with water, gabapentin is released by diffusion from the dosage form over a period of at least five hours and at least 40 wt% of the gabapentin is retained in the dosage form one hour after administration.

JTX 3 at col. 12, l. 38; col. 13, ll. 25-39; Stip. Facts¶ 70.

Dependent claims 34 and 62, respectively, add the following limitations: (i) the dosage form is administered once daily; and (ii) the mammal is a human. JTX 3 at col. 13, ll. 40-41; col. 14, ll. 50-53; Stip. Facts ¶¶ 71, 72.

b. U.S. Patent No. 7,731,989

United States Patent No. 7,731,989 (the "'989 Patent"), entitled "Gastric Retained Gabapentin Dosage Form," issued on June 8, 2010, to Depomed from a patent application filed on September 26, 2008, as a continuation of the '927 Patent. Stip. Facts ¶¶ 10, 73. The Orange Book identifies the expiration date of the '989 patent as October 25, 2022. Stip. Facts¶ 10. Gralise is an embodiment of the asserted claims of the '989 Patent. *Id.* ¶ 113.

Depomed has asserted claim 10 of the '989 Patent in this action. Stip. Facts ¶ 74. Claim 10 depends from claim 1, which has not been asserted. Claim 1 of the '989 Patent reads as follows:

> A dosage form, comprising between about 100 mg to about 4800 mg of gabapentin or pharmaceutically acceptable salt thereof, dispersed in a single polymer matrix comprising at least one swellable hydrophilic polymer that swells unrestrained dimensionally by imbibing water to increase its size to promote gastric retention of the dosage form in a stomach in a fed mode, wherein upon contact with water, gabapentin is released by diffusion from the dosage form over a period of at least five hours and at least 40 wt % of the gabapentin is retained in the dosage form 1 hour after administration.

JTX 4 at col. 12, ll. 9-18; Stip. Facts¶¶ 75-76. Claim 10 of the '989 Patent contains the additional limitation that "the gabapentin has a bioavailability greater than or equal to 80% of an equal dose of gabapentin in an immediate release dosage form." JTX 4 at col. 12, ll. 37-39; Stip. Facts ¶ 77.

c. U.S. Patent No. 8,192,756

United States Patent No. 8,192,756 (the "'756 Patent"), entitled "Gastric Retained Gabapentin Dosage Form," issued on June 8, 2010, to Depomed from a patent application filed on May 19, 2011, as a continuation of the '927 Patent, Stip. Facts ¶¶ 11, 78, and

claims the same priority date of October 25, 2001, JTX3 at 1. Depomed has asserted claims 1, 2, 5, 6, 7 and 11 of the '756 Patent in this action. Stip. Facts¶ 79. The Orange Book identifies the expiration date of the '756 patent as October 25, 2022. Gralise or its use in treating PHN embodies the asserted claims of the '756 Patent. *Id.* ¶ 114.

Claim 1 of the '756 Patent is directed to:

> A dosage form, comprising:
>
> comprising from 100 mg to 4800 mg of therapeutically effective amount of gabapentin or pharmaceutically acceptable salt thereof, dispersed in a single matrix
>
> wherein the matrix comprises at least one swellable hydrophilic polymer that swells unrestrained dimensionally by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach in a fed mode,
>
> wherein upon once-daily or twice-daily ingestion of the dosage form gabapentin is released from the matrix over a period of at least five hours wherein at least 40 wt% of the gabapentin is retained in the matrix one hour after administration, and
>
> wherein the gabapentin is released at a rate sufficient to achieve a lower maximum plasma concentration (C_{max}) compared to an equal dose of gabapentin provided by an immediate release dosage form, and without loss in bioavailability as measured by the area under the curve ($AUC_{infinity}$) as compared to the bioavailability which is achieved from an immediate release dosage form comprising the same dose of gabapentin.

JTX 5 at col. 12, l. 50 – col. 13, l. 3; Stip. Facts¶ 81.

Claims 2 and 5 depend from claim 1, and add the following limitations: (i) the time to reach maximum plasma concentration is longer relative to the time to reach maximum plasma concentration from an immediate release dosage form comprising the dose of gabapentin; and (ii) the dosage form comprises a dose of gabapentin of between about 300-600 mg. JTX 5 at col. 13, ll. 4-7, 12-13; Stip. Facts¶¶ 83, 84.

Claim 6 of the '756 Patent is similar to claim 1, however it is directed to a method of treating a condition using the gabapentin-containing dosage form:

> A method of treating a condition responsive to a therapeutic dose of gabapentin, comprising:
>
> orally administering once-daily or twice daily a dosage form comprising between about 100 mg to about 4800 mg of gabapentin or pharmaceutically acceptable salt thereof, dispersed in a single matrix,
>
> wherein the matrix comprises at least one swellable hydrophilic polymer that swells unrestrained dimensionally by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach in a fed mode, wherein upon once-daily or twice daily ingestion of the dosage form gabapentin is released from the matrix over a period of at least five hours wherein at least 40 wt% of the gabapentin is retained in the matrix one hour after administration, and
>
> whereby the dosage form releases gabapentin at a rate sufficient to achieve a lower maximum plasma concentration (C_{max}) compared to an equal dose of gabapentin provided by an immediate release dosage form, and without loss in bioavailability as measured by the area under the curve ($AUC_{infinity}$) as compared to the bioavailability which is achieved from an immediate release dosage form comprising the same dose of gabapentin.

JTX 5 at col. 13, ll. 14-38.

Claim 7 and 11 depend from claim 6, and add the following limitations: (i) the time to reach maximum plasma concentration is longer relative to the time to reach maximum plasma concentration from an immediate release dosage form comprising the dose of gabapentin; and (ii) the condition is neuropathic pain. JTX 5 at col. 14, ll. 1-4, 10-11.

d. U.S. Patent No. 8,252,332

United States Patent No. 8,252,332 (the "'332 Patent"), entitled "Gastric Retained Gabapentin Dosage Form," issued on August 28, 2012, to Depomed from a patent application filed on March 29, 2010, as a continuation of the '927 Patent. Stip. Facts ¶¶ 12, 88. Depomed has asserted claims 1, 6, 17, 22 and 24 of the '332 Patent. The Orange Book

identifies the expiration date of the '332 Patent as October 25, 2022. *Id.* ¶ 12. Gralise or its use in treating PHN embodies the asserted claims of the '332 Patent. *Id.* ¶ 115.

Claim 1 of the '332 Patent reads as follows:

> A dosage form, comprising a matrix comprising gabapentin, wherein upon ingestion of the dosage form gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a lower maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

JTX 6 at col. 12, ll. 12-22.

Claim 6 depends from claims 1, 4, and 5. Claim 4 is directed to "[t]he dosage form of claim 1, wherein the matrix is a polymer matrix." JTX 6 col 12, ll. 27-28. Claim 5 is directed to "[t]he dosage form of claim 4, wherein the polymer matrix is comprised of a swellable, hydrophilic polymer." *Id.* ll. 29-30. Claim 6 is directed to "[t]he dosage form of claim 5, wherein the gabapentin is released from the polymer matrix by diffusion." *Id.* ll. 31-32.

Asserted claim 17 is a method claim which depends from claim 12. Claim 12 of the '332 patent reads as follows:

> A method of treating a condition responsive to a therapeutic dose of gabapentin, comprising: orally administering a dosage form, comprising a matrix comprising gabapentin, wherein upon ingestion of the dosage form gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a lower maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasmaconcentration-time curve, AUC_{inf}.

JTX6 at col 12, ll. 53-65. Claim 17 adds the limitation that the "condition is neuropathic pain." *Id.* col. 13, ll. 6-7.

Claim 22 of the '332 Patent is directed to:

> A dosage form, comprising a matrix comprising gabapentin, wherein upon ingestion of the dosage form gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a longer time to the maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

JTX 6 at col. 13, l. 21 - col. 14, l. 2.

Claim 24 of the '332 Patent is directed to:

> A method of treating a condition responsive to a therapeutic dose of gabapentin, comprising orally administering a dosage form comprising a matrix comprising gabapentin, wherein gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a longer time to the maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

JTX 6 at col. 14, ll. 16-29.

e. U.S. Patent No. 8,333,992

The '992 Patent, entitled "Gastric Retained Gabapentin Dosage Form," issued on December 18, 2012, to Depomed from a patent application filed on July 27, 2012, as a continuation of the '927 Patent. Stip. Facts ¶¶ 13, 99. The Orange Book identifies the expiration date of the '992 Patent as October 25, 2022. *Id.* ¶ 13. Gralise or its use in treating PHN embodies the asserted claims is an embodiment of the '992 Patent. *Id.* ¶ 116.

Depomed has asserted claims 1, 5 and 22 of the '992 Patent in this action. Stip. Facts¶ 100.

Claim 1 of the '992 Patent is directed to:

> A dosage form, comprising a matrix comprising gabapentin, wherein upon ingestion of the dosage form by a human subject gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a lower maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUCinf.

JTX 7 at col. 12, ll. 40-51; Stip. Facts ¶ 102.

Claim 5 depends from claim 4, which in turn depends from claim 1. Claims 4 and 5, respectively, add the limitations "wherein the matrix is a polymer matrix" and "wherein the polymer matrix is comprised of a swellable, hydrophilic polymer." JTX 7 at col. 12, ll. 56-59.

Asserted Claim 22 of the '992 Patent reads as follows:

> A method of treating a condition responsive to a therapeutic dose of gabapentin, comprising: orally administering to a human subject a dosage form comprising a matrix comprising gabapentin, wherein gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a longer time to the maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

JTX 7 at col. 14, ll. 13-26.

D. WITNESSES AT TRIAL

The trial commenced with Plaintiff's infringement case. For its infringement case-in-chief, Depomed called five expert witnesses, Dr. Eden Tesfu, Dr. Gary Annunziata, Dr. Hartmut Derendorf, Dr. Robert O. Williams, and Dr. Howard Hopfenberg.

Dr. Eden Tesfu, a former laboratory manager at Evans Analytical Life Sciences, was accepted by the Court as an expert in analytical chemistry. Tr. 92:19-22. Dr. Tesfu testified regarding swelling and dissolution studies performed on the Defendants' proposed ANDA product and Plaintiff's Gralise tablet. Tr. 89-134.

Dr Gary Annunziata, a practicing gastroenterologist at the Eisenhower Medical Center, Palm Springs, California, was accepted by the Court as an expert in stomach physiology. Tr. 148:12-14. Dr. Annunziata testified with respect to the human pylorus and the process of stomach digestion and emptying. Tr. at 141-168, 207- 260.

Dr. Hartmut Derendorf, a professor of pharmaceutics at the University of Florida, was accepted as an expert in the field of pharmacokinetics by the Court. Tr. at 336:5–8. Dr. Derendorf testified on the pharmacokinetic data from the Actavis ANDA and evidence for gastric retention. Tr. at 332-367. Dr. Derendorf also provided testimony with respect to the issue of obviousness. Tr. at 1022-1061.

Dr. Robert O. Williams, a professor at the University of Texas and a registered pharmacist in the State of Texas, was accepted by the Court as an expert in the field of formulation and pharmaceutical sciences. Tr. at 264:4–7. Dr. Williams testified as to the ingredients and swelling properties of the proposed ANDA product and Gralise tablets. Tr. at 260-309.

Dr. Harold Hopfenberg, a professor of chemical and biomolecular engineering at North Carolina State University, was accepted by the Court as an expert in polymer science and controlled release dosage forms. Tr. at 437:13-19. Dr. Hopfenberg testified as to the shape and swelling of the Actavis ANDA product. Tr. at 431-494. Dr. Hopfenberg also testified with respect the obviousness issues relating to the '962 Patent in Depomed's response case. Tr. at 931-955.

Plaintiff also presented the testimony of three fact witnesses with respect to the issue of infringement, Mr. Jack Lee Anders, VP of Finance for Depomed Inc., Dr. Radi Hejazi, Formulation Scientist at Actavis Elizabeth, and Dr. Meena Venugopal, former employee at Actavis.

In response to Plaintiff's infringement case, Defendant called one expert witness, Dr. David Friend, director of product development at the CONRAD Program and associate research professor of obstetrics and gynecology at Eastern Virginia Medical School. Dr. Friend was accepted as an expert in the design and development of controlled release dosage forms, design and development of gastric retained dosage forms, behavior of dosage forms in the stomach during fed mode and the sizes and shapes of oral dosage forms. Tr. 498:9-12, 502:3-504:10. Dr. Friend testified as to the shape and swelling of Defendant's ANDA tablets. Tr. 497-547.

The trial then proceeded to the issue of validity. Defendant's obviousness case-in-chief was presented through two expert witnesses, Dr. Douglas Flanagan and Dr. Michael Mayersohn, along with a fact witness by way of deposition testimony, inventor Dr. Sui Yuen Eddie Hou (by video), a former Depomed employee and one of the named inventors of the Gabapentin Patents.

Dr. Douglas R. Flanagan, a professor emeritus of pharmacy of the University of Iowa and the chief scientific officer for the University of Iowa's Pharmaceuticals Development Consortium, was accepted as an expert in pharmaceutical formulation, including the design and development of controlled release dosage forms. Tr. 549:20-22, 552:10-14. Dr. Flanagan provided testimony on the issue of obviousness with respect to all of the Gabapentin Patents ('927, '989, '756, '332, '992 Patents). Tr. 549-578, 608-687.

Dr. Michael Mayersohn, a professor of pharmaceutical sciences at the University of Arizona, College of Pharmacy, was accepted as an expert on drug absorption and pharmacokinetics. Tr. 688:14-15, 692:6-10. Dr. Mayersohn testified on the issue of obviousness with respect to two of the Gabapentin Patents, the '332 and '992 Patents. Trial Tr. 688-742.

In its response to Defendant's obviousness case, Plaintiffs called experts Dr. Howard Bockbrader, Dr. Barry Gidal, Dr. Michelle Brown, Dr. Howard Hopfenberg, Dr. Linda Felton, Dr. Hartumut Derendorf, and Dr. Sean Nicholson. Plaintiff also presented testimony by deposition of Dr. Andrew Johnson, Analytical Scientist for Actavis, regarding his role in the development of the ANDA product. Tr. 1138:2-8.

Dr. Howard Bockbrader was accepted by the Court as an expert in the area of clinical pharmacokinetics and in particular the pharmacokinetics of gabapentin. Trial Tr. 748:8-13. Dr. Bockbrader testified with respect to Warner-Lambert efforts to develop an extended release gabapentin product and its opinion as to whether a gastric retained gabapentin product could be developed. Tr. at 743-777. His testimony related to the '927, '989, '756, '332 and '992 Patents.

Dr. Barry Gidal was accepted by the Court as an expert on gabapentin pharmacokinetics and pharmacodynamics. Trial Tr. 815:14-816:2. Dr. Gidal testified on issues related to whether it was possible to develop a controlled-release gabapentin tablet. Tr. at 811-865. His testimony related to the Gabapentin Patents.

Dr. Michelle Brown was accepted by the Court as an expert in the area of treating neuropathic pain. Tr. at 869:4-20. Dr. Brown testified on the issue of long felt need for a controlled-release gabapentin product and the manner in which Gralise is prescribed. Trial Tr. at 866-893. Her testimony related to the Gabapentin Patents.

Dr. Linda Felton was accepted by the Court as an expert in controlled- release dosage forms. Tr. at 959:1-4. Dr. Felton testified regarding non-obviousness of a controlled-release gabapentin tablet. Tr. at 955- 1021. Her testimony related to the Gabapentin Patents.

Dr. Sean Nicholson was accepted by the Court as an expert in the field of economics in healthcare. Tr. at 1064:5-7. Dr. Nicholson testified as to his evaluation of the commercial success of the Gralise product, the '962 Patent and the Gabapentin Patents. Tr. at 1061-1099.

In rebuttal, Defendant called two expert witnesses, Dr. Raymond Sinatra and Dr. Ryan Michael Sullivan.

Dr. Raymond Sinatra was accepted by the Court as an expert in pain medicine and the prescribing practices of physicians in pain management. Tr. At 895:21-24. Dr. Sinatra testified as to clinical trials performed on Gralise. Tr. at 893-908.

Dr. Ryan Michael Sullivan was accepted by the Court as an expert in the economics of intellectual property as it pertains to pharmaceutical products. Tr. at 1165:25-1166:5.

Dr. Sullivan testified as to his evaluation of the commercial success of Gralise. Tr. at 1164-1201.

E. INFRINGEMENT

1. Legal Standards

If an ANDA seeks approval for a drug that is claimed in a patent or the use of which is claimed in a patent, submission of the ANDA constitutes a statutory act of infringement pursuant to § 271(e)(2) of the Patent Act. This section provides:

> It shall be an act of infringement to submit an application under [section 355(j) of title 21] ... for a drug claimed in a patent or the use of which is claimed in a patent ... if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

35 U.S.C. § 271(e)(2)(A). In order make the infringement determination, a court conducts a two-step infringement inquiry. First, the court construes the claims of the patent. Second, the court compares the construed claims to the accused product and makes a determination as to whether every claim limitation, or its equivalent, is found in the accused product. *Roche Palo Alto LLC v. Apotex, Inc.*, 531 F.3d 1372, 1377 (Fed. Cir. 2008). In the ANDA context, the proper infringement inquiry focuses on the actual product that will enter the market upon FDA approval. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) (court "must focus on what the ANDA applicant will likely market if its application is approved"); *Ben Venue Labs. v. Novartis Pharm. Corp.*, 146 F.Supp.2d 572, 579 (D.N.J. 2001) ("the statute requires that an infringement inquiry be focused on what is likely to be sold following FDA approval").

To prove infringement, the patentee must show that an accused product or method is within the claim limitations of the patent-in-suit either literally or under the doctrine of equivalents. *See Amgen Inc. v. F. Hoffmann-LaRoche Ltd.*, 580 F.3d 1340, 1374 (Fed. Cir. 2009); *Warner Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997).

Direct infringement requires a party to perform each and every step or element of a claimed method or product. *Cheese Systems, Inc. v. Tetra Pak Cheese and Powder Systems, Inc.*, 725 F.3d 1341, 1348 (Fed. Cir. 2013). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989).

Induced infringement, on the other hand, "requires that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). The induced infringement provision of the Patent Act, 35 U.S.C. § 271(b), provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." "[T]he sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent, and usually is also contributory infringement." *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 Fed. App'x 917, 926 (Fed. Cir. 2011) (citing *Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010); *DSU Med. Corp.*, 471 F.3d at 1305–06.

Thus, induced infringement under § 271(b) occurs where: (1) another party directly infringes a patent claim; (2) the inducing party intentionally encourages the acts that constitute such direct infringement; and (3) the inducing party knows that its actions will

cause direct infringement. *See Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1312 (Fed. Cir. 2005). To prove indirect infringement by the manufacturer of an allegedly infringing product, a patentee must show that the manufacturer's customers directly infringe the patent. *See Glenayre Elecs., Inc. v. Jackson*, 443 F.3d 851, 858 (Fed. Cir. 2006). Induced infringement under 35 U.S.C. § 271(b) requires knowledge that the induced acts constitute patent infringement. *See Global-Tech*, 131 S. Ct. at 2068.

Contributory infringement occurs if a party sells or offers to sell, a material or apparatus for use in practicing a patented process, and that "material or apparatus" is material to practicing the invention, has no substantial non-infringing uses, and is known by the party "to be especially made or especially adapted for use in an infringement of such patent." 35 U.S.C. § 271(c). Contributory infringement exists where "it may be presumed from distribution of an article in commerce that the distributor intended the article to be used to infringe another's patent, and so may justly be held liable for that infringement." *Metro–Goldwyn–Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 932 (2005).

To establish contributory infringement, the patent owner must prove that: "(1) there is direct infringement; (2) the accused infringer had knowledge of the patent at issue; (3) the component has no substantial noninfringing uses; and (4) "the component is a material part of the invention." *See Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010).

An accused infringer's knowledge of the patents may be demonstrated by an ANDA filer's certification and Notice Letter to the patent holder. *Teva Pham. U.S.A., Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295, 349 (S.D.N.Y 2012).

In assessing whether an asserted noninfringing use is substantial, the factfinder considers not only the use's frequency, but also the use's practicality, the invention's intended purpose, and the intended market. *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 851 (Fed. Cir. 2010) aff'd, 131 S. Ct. 2238, 180 L. Ed. 2d 131 (2011). A substantial non-infringing use is one that is "not unusual, farfetched, illusory, impractical, occasional, aberrant, or experimental." *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009).

Plaintiff bears the burden of proving infringement and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

2. Direct Infringement

a. The '927, '989, and '756 Patents

Plaintiff alleges direct, literal infringement of the '927, '989, and '756 Patents. With respect to infringement of these patents, there is a single claim element that is in dispute, specifically, "swells … to increase its size to promote gastric retention." The Court has construed this claim element, which appears in several of the asserted patents, to mean "such that when the dosage form is introduced into the stomach in the fed mode, the dosage form remains in the stomach for several hours." D.I. 251 at 6-11. Claims 18, 25, 26, 34, 61 and 62 of the '927 Patent, claims 1, 2, 5, 6, 7 and 11 of the '756 Patent and claim 10 of the '989 Patent each contain this claim element. Tr. 519:13-520:25. The Court finds that Plaintiff has established by the preponderance of the evidence that Defendant's ANDA product meets this limitation.

As an initial matter, the proposed ANDA products use hydrophilic polymers known to swell in gastric fluid. Indeed, the proposed ANDA labeling states that the gabapentin tablets swell in gastric fluid and gradually release gabapentin. Tr. 457:16-18; PTX000136, ACTGAB000321121. According to the label, the ANDA products contain [redacted] Tr. 163:4-17; PTX000136, ACTGAB000321121. They [redacted] Tr. 271:17–22; PTX000014, ACTGAB000000330. [redacted] hydrophilic, *i.e.*, "water loving", and are known to absorb water and swell. Tr. 458:5-23; *see also* Tr. 270:10–271:8; PTX0-136, ACTGAB000321121. Thus, the tablets swell in gastric fluid and contain ingredients that are swellable or imbibe water. Tr. 163:4–17; 238:18-239:3.

Second, the ANDA products use similar swellable polymers in similar amounts as Gralise tablets, which are embodiments of the asserted claims. *See* PTX000014 at ACTGAB000000330, [redacted] according to Dr. Williams, are considered to be enabling of diffusion controlled release from a tablet dosage form. Tr. 271:17-22; 273:1-9. The higher the molecular weight of the polymer used in a dosage form, the more that dosage form tends towards diffusion control of the drug. Tr. at 270:23 – 271:8.

The ANDA products [redacted] in the Gralise tablet. Tr. 273:10-23; PTX000014. These [redacted] both hydrophilic swellable polymers acting

in conjunction [redacted] release resulting in the slow diffusion of gabapentin. Tr. 273:10-23; PTX000014.

Gralise and the ANDA products use similar percentages of hydrophilic polymers. Tr. 274:11 – 275:16; PTX000014, ACTGAB000000330. The ANDA product contains [redacted] weight of water-soluble swellable hydrophilic polymers and [redacted] weight of water-soluble swellable hydrophilic polymers. *Id.* These percentages of polymers indicate that both tablets release gabapentin by the process of diffusion. *Id.*

Third, the parties have stipulated that the ANDA products release gabapentin by diffusion, Stip. Facts ¶¶ 3, 5, 7, and 11, and according to Plaintiff's expert Dr. Williams, the diffusion of highly soluble drugs, like gabapentin, is controlled through the use of high molecular weight hydrophilic swellable polymers that wet, gel, and swell, Tr. 265:9-19. As explained by Dr. Williams, these swellable, hydrophilic polymers serve as a diffusion barrier. The highly water-soluble gabapentin quickly dissolves yet slowly diffuses through the polymer viscous layer. *Id.* It is the swelling of the hydrophilic polymers that controls the diffusion of highly soluble drugs like gabapentin out of the dosage form. Tr. 266:21–24.

Release of a crystalline drug like gabapentin from a controlled release dosage form like the ANDA products requires the ingress of water into the dosage form, which according to Dr. Hopfenberg, changes the nature of the dosage from to a softer, swollen form. Tr. 453:16 – 454:14. Dr. Williams explained that if Defendant's products were not

swelling, the release would be similar to an immediate release tablet because there would be no barrier formed by the swelling and hydrating polymers. Tr. 279:1-7.

The proposed labeling for the ANDA products states that the "[g]abapentin tablets swell in gastric fluid and gradually release gabapentin." PTX000136, ACTGAB000321121. This tells one skilled in the art that the ANDA products are extended release and the mechanism of gabapentin release is by diffusion. Tr. 274:2 – 277:1.

Fourth, *in vitro* studies show unrestrained swelling and mass gain consistent with water uptake in the ANDA [redacted]. 459:4-18; Trial Tr. 166:12–167:24; 255:1-23; PTX000135, ACTGAB000320623. These studies compared the mass of the 300 mg and 600 mg ANDA products to similar dosage sizes of Gralise after incubation in simulated gastric fluid. The results showed that the 300 and 600 mg ANDA products [redacted] 460:3-461:7; 64:22-24, 66:24-67:7; 277:7–24, 278:6–15; PTX000135 (specific weight gain data). [redacted]. 207:2–208:14.

These studies also compared the dimensions of the 300 mg and 600 mg Actavis ANDA products to similar dosage sizes of Gralise after incubation in simulated gastric fluid, and the [redacted] 461:10-19; Trial Tr. 62:16 – 63:25, 66:24 – 67:7; PTX000135; Tr. 208:15–209:21; 277:7-24. [redacted]

[redacted] (setting forth specific measurement data). As Dr. Annunziata testified, the increases in length, thickness and width of the tablets are significant and decrease the chances of the tablets passing through the pylorus[4] in fed state. Tr. 208:15 – 209:21.

Similarly, swelling studies performed by Evans Analytical Group ("EAG") on the ANDA product show that the tablets increase in size and mass when incubated in water or simulated gastric fluid. Tr. 462:7-463:4; PTX000238, *see also* Tr. 278:16–25, 279:8-19; 211:20 – 212:21. EAG's data show that Actavis' 600 mg [redacted] 212:22 – 213:9; PTX000238 (data for 600 mg tablet). [redacted] PTX000238 (data for the 300 mg tablet). The increase in mass and size each for these tablets make it more likely that the tablet will be retained in the stomach in fed mode. Tr. 212:22–213:17; 214:6–21.

The Court gives little weight to Dr. Friend's testimony criticizing the results of the above swelling studies as having no relevance because they do not accurately reflect conditions in the fed stomach. Dr. Friend contends that the studies fail to account for more

[4] The pylorus is the structure in the stomach that regulates materials leaving the stomach into the intestine. Tr. 152:16-153:1. In the fed mode, the pylorus is generally, tightly clenched closed in order to prevent food from moving into the intestine before it is broken down into small particles. Tr. 152:19-23. Periodically, the pylorus relaxes and opens, allowing some of the stomach contents to pass from the stomach into the intestine. Tr. 235:9-19.

of the destructive forces in the stomach during fed mode. Tr. 522:1-8. The Court credits Dr. Williams testimony, however, stating that if the action of the stomach were grinding down or breaking the ANDA products *in vivo*, it would result in a much faster release of the gabapentin and change the pharmacokinetic data. Tr. 267:3-18; 302:15 – 303:5. That is, if the dosage form were being ground down *in vivo*, the tablet would not have the ability to release gabapentin over the extended period of five hours through the process of diffusion as the parties have stipulated that it does in accordance with, *e.g.*, claim 17 of the '927 Patent. Stip Facts at ¶¶ 5, 7 and 9; Tr. 267:3-18; JTX003, JTX004. Additionally, the parties further stipulated that the ANDA products "remains substantially intact until substantially all of said drug is released" as claimed in the '280 Patent. Stip. Facts ¶ 3; JTX002.

Fifth, the Court finds credible the expert testimony of Dr. Williams who opined that the ANDA products have "at least one swellable hydrophilic polymer that swells in a dimensionally unrestrained manner by imbibing water to increase its size" as required by (i) asserted claims 18, 25, 26, 34, 61 and 62 of the '927 Patent, (ii) asserted claims 1, 2, 5, 6, 7 and 11 of the '756 Patent, and (iii) asserted claim 10 of the '989 Patent. Tr. 268:10 – 269:14. This opinion is based on and is consistent with the findings above.

Sixth, the evidence shows that the swelling of the ANDA product promotes gastric retention in the stomach. Dr. Annunziata provided testimony as to the workings of the stomach in the fed mode, the state in which the stomach is to be in when the ANDA product is taken. Upon the intake of food, the stomach enters the fed mode, during which the stomach reduces large pieces of food into smaller pieces. Tr. 151:13-15. During fed mode, the pH of the stomach changes and the stomach begins to contract. Tr. 152:14-18.

Waves of contractions start at the top (the fundus) and proceed through the stomach to the antrum while the pylorus is clenched. *Id.* The pylorus retains large particles in the stomach so that they can be further digested, and it allows smaller particles, those measuring about 2-4 mm, to pass through to the small bowel. Tr. 154:8-13, 217:16 – 218:4. The pylorus is closed during the terminal antrum contraction and is open for brief periods of time during the retropelling wave in which it opens like a relief valve to approximately 12.8 millimeters. Tr. 144:25 – 145:11, 155:10-18; 159:9-13, 233:18 – 234:1. The retropelling wave pushes the remaining particles back up into the body of the stomach to then repeat the process. Tr. 152:9 – 153:1, 153:13-15. The length of time the stomach is in fed mode varies; fed mode may last anywhere between 45 minutes and six hours depending upon the meal ingested. The average time is approximately four hours. Tr. 230:4-21.

According to Dr. Annunziata, it takes longer for meals of larger weight or higher calorie content to empty from the stomach. Tr. 257:12-15; PTX000469. Indeed, the density, weight, or shape of a particle may make it more difficult for that particle to exit the stomach. Tr. 156:15–18. It logically follows, therefore, that a larger or swollen particle is less likely it is to leave the stomach. Tr. 155:19-22, 156:4-11, 158:16-20, 209:5-21. Dr. Annunziata explained that as a particle approaches the size of one centimeter, it becomes very unlikely for it to leave the stomach through the pylorus. Tr. 156:4-11. A particle with an elongated shape is likely to be repulsed from the pylorus when the stomach clenches and is retropelled back into the stomach. Tr.156:15-23, 158:14-15. An increase in the mass of a particle also makes it more likely to be retained. Tr. 218:20-22.

The above-referenced swelling studies show that the each of the ANDA product tablets increases in both dimension and weight. Consequently, as the swelling tablet

approaches the pyloric channel it will tend to be retropelled, *i.e.*, pushed back to the top of the stomach when the pyloric channel clenches. Tr. 218:5-13. While a long tablet is likely to be retained even when the pylorus is open because it may approach the pylorus sideways, Tr. 219:1-10, the increase in size of the short axis also makes it less likely that the tablet will pass through the pylorus, Tr. 219:11-16.

Seventh, according to the instructions on the ANDA product's proposed label and the pharmacokinetic data, a person of skill in the art would understand that the ANDA tablets remain in the stomach for several hours. In this regard, some background as to how gabapentin is absorbed by the body is useful. Studies have shown that gabapentin absorption takes place in primarily in the small intestines. Tr. 339:11-16; PTX000500 at Gralise_JDG_00000602. The *Stevenson* reference states "[c]omparison of the blood-level data from oral and jejunal administration of gabapentin indicates that there is substantial absorption from the duodenum and upper jejunum. Most important, gabapentin plasma levels from colonic administration are substantially lower than those obtained from oral and upper intestinal administration." Tr. 339:17 – 340:2; PTX000500 at Gralise_JDG_ 00000602.

Gabapentin "transporters," which are proteins that "take up" the drug and move it to the other side of the intestinal membrane, are located only in a small range of the small intestine and, therefore, gabapentin must be "at the right place at the right time" in order to be to be taken up. Tr. 338:5-13, 337:2 – 338:3. If the dosage form passes by the window of absorption too rapidly (*i.e.*, before the drug is released), the dosage form will not work well because gabapentin will be released into the large intestine where it is not absorbed. Tr. 340:20-24.

Also, because gabapentin transporters are present in limited numbers, too much drug saturates them, preventing further drug uptake. Tr. 339:3-8. Upon transporter saturation, the uptake of gabapentin will no longer go up proportionately with an increase of gabapentin dose. Although the amount of gabapentin provided may go up, the percent absorption will go down. Tr. 341:14-24.

While gastric emptying time is affected by food, small intestinal transit time is not. Tr. 344:3-13; Tr. 345:15 – 346:8; PTX000521 at DEPOACT0982017. It takes approximately three hours for a dosage form to pass through the small intestines. Tr. 340:15-19; Tr. 343:12 – 344:10; PTX000525 at DEPOACT0981978-981980; 345:10-24; PTX000521 at DEPOACT0982017.

In the case of a gastric-retained dosage form, the dosage form remains in the stomach and releases the drug from that location. The drug moves down from the stomach over a long period of time to the small intestine and can be absorbed by transporters there. Tr. 338:23 – 339:2. Without gastric retention, the dosage form will leave the stomach earlier and move into the small and large intestines. Thus, without gastric retention, there would be a much earlier T_{max} (*i.e.*, time to maximum concentration of the drug in the subject's blood plasma, Tr. 315:20-24, 316:11- 14) and incomplete absorption because the drug would be released when it is no longer able to be absorbed in the upper small intestines. Tr. 349:2-14. With respect to gabapentin, gastric retention is essential for sustained exposure of gabapentin to its site of absorption in the upper small intestines, and this can be achieved by anchoring the dosage form in the stomach allowing the drug to come out of the dosage form slowly over time. Tr. 344:18 – 345:6.

The proposed labeling for the ANDA products states "gabapentin should be titrated to an 1800 mg dose taken orally once-daily with the evening meal. Gabapentin tablet should be swallowed whole. Do not crush, split or chew the tablets." PTX000136, DEPOACT0321105. This labeling also states "[g]abapentin should be taken with evening meals. If it is taken on an empty stomach, the bioavailability will be substantially lower." *Id.*, DEPOACT0321123. Dr. Annunziata explained that one skilled in the art understands that when medication is given during the evening meal, it is typically intended for the dosage form to be retained in the stomach. Tr. 220:1-11. Medication given during fasting state is generally expelled quickly from the stomach and, in the case of gabapentin, this would limit its ability to be absorbed. Tr. 163:22 – 164:11.

The proposed labeling further states "gabapentin is absorbed from the proximal small bowel by a saturable L amino transport system. Gabapentin bioavailability is not dose proportional. As the dose is increased, bioavailability decreases." PTX000136, ACTGAB000321122. This informs one of skill that the drug ends up in and is absorbed at the small bowel, which is the duodenum and upper jejunum, after being released from the stomach where the dosage form resides. Tr. 165:10-21.

Thus, based on the label, a person of skill in the art would understand that if the gabapentin tablet is given outside of a meal, it will leave the stomach during the digestive process and therefore the gabapentin will not have time to be absorbed before it passes through the area in the small bowel where it is absorbed. Tr. 164:12 – 165:1. The label's fed mode requirement, therefore, is an indication that the tablet is intended to stay in the stomach. Tr. 217:6-15.

That the dosage remains in the stomach for several hours when administered according to the fed requirement is shown by the pharmacokinetic data. Plaintiff's expert Dr. Derendorf, an expert in the area of pharmacokinetics, explained that pharmacokinetic data shows that the ANDA products are retained in the stomach. Tr. 332-67. Defendant had two bioequivalence studies performed on the 600 mg ANDA tablet that compared it to Gralise--one study was done under fasting conditions while the other was done with the stomach in fed mode. 315:2-8, 327:7 – 328:9; 319:13 – 320:1. Under fasting conditions the 600 mg Actavis ANDA Product achieved an average C_{max} (*i.e.*, the maximum concentration the drug reaches in blood plasma after administration) of 1.87 + 0.752 μg/ml and the Gralise 600 mg product achieved a C_{max} of 1.81 μg/ml. Tr. 316:16 – 317:7; PTX000019 at ACTGAB000000555. In the fasted state the ANDA Product had a median T_{max} of four hours and Gralise 600 mg had a median T_{max} of 3.5 hours. Tr. 317:21 – 318:1; PTX000019 at ACTGAB000000555. The 600 mg ANDA Product had an AUC (i.e., "area under the curve" measured from time zero to the last blood draw point of the study and references the exposure of the drug in the subject, Tr. 316:3-7, 315:25 – 316:2) of 20.91 + 9.55 μg/ml and the Gralise 600 mg tablet had an AUC of 19.14 + 7.643 μg/ml. Tr. 318:9-18; PTX000019 at ACTGAB000000555.

Under fed conditions the 600 mg Actavis ANDA Product achieved a C_{max} of 3.47 + 0.652 μg/ml and Gralise 600 mg tablets achieved a C_{max} of 3.48 + 0.573 μg/ml. Tr. 320:2-15; PTX000020 at ACTGAB000000581. The median T_{max} of the 600 mg Actavis ANDA Product is 10 hours under fed conditions and the median T_{max} of the Gralise 600 mg tablets is 9 hours. Tr. 320:19-321:1; PTX000020 at ACTGAB000000581. Under fed conditions

the average AUC is 55.26 μg/ml for the 600 mg ANDA product and AUC is 52.20 μg/ml for the Gralise 600 mg tablets. PTX0000020 at ACTGAB000000581.

Thus, test subjects given the 600 mg ANDA Product achieve a C_{max} of 1.87 in fasting, and this increased to 3.47 under fed conditions. Tr. 321:8-15. The median T_{max} of subjects given the 600 mg Actavis ANDA Product was 4 hours in fasting and 10 hours in fed mode. Tr. 321:16-22. Overall, the results of the studies are consistent with the dosage form being gastric retained during the fed mode. Tr. 349:18 – 350:16, 346:25 – 348:21; PTX000506; 328:1-9; Tr. 348:22 – 349:14; 349:18 – 350:16; PTX000034; Tr. 327:11-22. The data on 600 mg ANDA tablet data in fed conditions shows that there is drug coming from the stomach over several hours, which is consistent with gastric retention of the dosage form. Tr. 348:1-21; PTX0000034 at ACTGAB000008356.

Testing was also performed on the 300 mg ANDA product under fasting conditions only, which indicated no gastric retention during such conditions. Tr. 326:17–25; PTX000023 at ACTGAB000000659. Actavis submitted a waiver for 300 mg fed studies indicating that the it was not necessary because the once daily 300 and 600 mg tablets are proportionally similar, Tr. 356:3–18, and pointing out that that the 300 and 600 mg ANDA tablets have dissolution rates that are similar to the Gralise 300 and 600 mg tablets. Tr. 356:21–357:13.

Dissolution studies show that the ANDA products have the same dissolution rates and pharmacokinetics as the Gralise tablets, which the parties agree are embodiments of the ‘927, ‘989 and ‘756 Patents and are gastric retained. Tr. 357:3-359:20; PTX 12. That the ANDA products have the same dissolution rates and pharmacokinetics as the Gralise tablets is indicative of these tablets having the same mechanisms (e.g., gastric retention, absorption

rates), otherwise differences in the blood levels or dissolution rates would be seen. Tr. 357:17– 359:2.

Finally, the Court credits the testimony of Drs. Derendorf and Annunziata, who based on the foregoing, opined that the ANDA products increase its size to promote gastric retention of the dosage form within the meaning of the asserted claims of the '756, '927 and '989 Patents. Tr. 336:20 – 337:6, 359:3-19; 162:1-10; 217:1-5; 219:17 – 221:18.

Defendant argues that evidence merely showing gastric retention of the ANDA tablets does not show that there has been the required swelling of the tablet in the stomach, as Defendant contends there is evidence that something other than swelling causes the ANDA product to remain in the stomach. *E.g.*, Tr. 235:9-19 (small particles can be retained in the stomach); 129:22-25; PTX 332 at DEPOACT0975179.1 (ANDA tablets began floating during testing). However, the Court finds that the preponderance of the evidence set forth above shows that Defendant's ANDA product "swells … to increase its size to promote gastric retention," as that term has been construed by this Court. Consequently, based on the foregoing, the Court concludes that a preponderance of the evidence shows that Defendant's 300 mg and 600 mg ANDA products will, if produced and marketed, directly infringe claim 10 of the '989 Patent; claims 1, 2, and 5 of the '756 Patent; claims 1, 6 and 22 of the '332 Patent; and claims 1 and 5 of the '992 Patent.

b. The '280 Patent

Actavis has stipulated that its 300 mg and 600 mg ANDA products meets all the elements of the asserted claims except one. Claim 1 of the '280 Patent requires that "said dosage form being one that when swollen … is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode." JTX 2 at col. 17,

ll. 53-55; Stip. Facts¶ 53. Claims 12, 14, and 45 are dependent upon claim 1. JTX 2; Stip. Facts¶ 52. Thus, claims 1, 12, 14, and 45 of the '280 Patent require that the "dosage form … when swollen" be "a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode." Defendant first argues that this claim is indefinite, and for the reasons set forth in a later section of this opinion, the Court finds that it is not indefinite. The parties also dispute, if not indefinite, whether this limitation is met.

The person of ordinary skill in the art understands the claim phrase "said dosage form being one that when swollen" in Claim 1 of the '280 Patent to mean that the claimed dosage form swells by the imbibition of water so that it increases in size. Tr. 455:3-23. There appears to be little dispute in that regard. And as noted earlier, the Court has construed "is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode" to mean "such that when the dosage form is introduced into the stomach in the fed mode, the dosage form remains in the stomach for several hours." D.I. 251 at 8-9.

As to the first portion of the disputed claim limitation, the evidence shows that the ANDA products swell. The Court discusses swelling above. Based upon his analysis of the Actavis product label, in vitro swelling studies conducted on the 300 mg and 600 mg ANDA products, and stipulations by Defendants that drug release from the ANDA dosage forms is controlled by diffusion, Dr. Hopfenberg credibly opined that the Actavis ANDA products swell and, therefore, satisfy the requirement "said dosage form being one that when swollen" in Claims 1, 12, 14, and 45 of the '280 Patent. Tr. 453:8 – 454:14; 457:1–464:5; PTX000135; PTX000136; PTX000238.

Based upon an analysis of the Actavis product label and multiple in vitro swelling studies conducted on the 300 mg and 600 mg ANDA products, Dr. Annunziata credibly opined that the ANDA products will remain in the fed stomach for several hours following ingestion. Tr. 222:4 – 223:10; PTX000135; PTX000136; PTX000238. Dr. Derendorf testified, based upon his analysis of pharmacokinetic data obtained from Gralise and from the 300 mg and 600 mg Actavis ANDA products, that the ANDA products are gastric retained within the meaning of the asserted claims of the '280 Patent. Tr. 349:18 – 351:16, 354:9 – 356:2, 357:17 – 359:2, 359:20-22.

Defendant argues that its ANDA products do not infringe because Plaintiff has failed first to established that the ANDA products swell and, second, that even if there was proof of swelling, there is no evidence that such swelling exceeds the size of the pyloric diameter.[5]

As to Defendant's first argument, the Court has concluded, *supra*, that the evidence establishes that Defendant's ANDA products swell. Defendant's second argument also fails in that it ignores the claim construction adopted by the Court. In any event, even if a size limitation were considered, the evidence shows that it is more likely than not that the ANDA products swell to a size that exceed the pyloric diameter. Actavis reported swelling data to the FDA showing that its tablets swell in vitro in simulated gastric fluid:

[5] Pyloric diameter here refers to those periods that the pylorus relaxes to allow larger materials to escape the stomach, and not the periods of time during which the pylorus is clenched tightly closed to prevent the stomach contents from being expelled into the intestines.

PTX 135 at ACTGAB000320624. Dr. Annunziata testified based upon his review of this experimental data that the 600 mg ANDA product "becomes a very large tablet" and the 300 mg ANDA product "gets to be a fairly large tablet," Tr. 223:12 – 224:3; *see also* 208:16 – 209:21, 218:5 – 219:10. As a result of this swelling, Dr. Annunziata testified that, based upon the what is known in the art as well as his own personal "almost daily" observations of the size of the human pylorus, the 300 mg tablet is "going to be less likely to go across the pyloric channel" and the 600 mg tablet similarly is "less likely to traverse the pyloric channel" and that the size of the dosage forms exceed the diameter of the pylorus. Tr. 208:12 - 209:21; 210:21 - 211:2; 224:16-20.

Data available from scientific publications suggests that the pyloric diameter is 12.8 mm ± 7.0 mm, or a range of 5.8 mm to 19.8 mm. Tr. 242:24-243:4, 244:16-246:18; 527:11-528:9; PTX 245. Dr. Annunziata testified that the size can vary from person to person due to anatomy or disease, but in his experience he typically sees pyloric diameters being about 10 mm (*i.e.*, 1 cm). Tr. at 247:15-19. In either case, the data shows that the

300 and 600 mg tablets exceed these measurements, in the fed mode, which testimony shows could be up to three or four hours or more. Tr. 230:4-21; 532:11-15.

Finally, Defendant contends there is no infringement with regard to the 600 mg tablet because it notes that the dry tablet starts out at a size larger than the pyloric diameter and, therefore, swelling is not responsible for its dimensions being larger than the pyloric diameter. Without finding whether the 600 mg tablet does or does not have a dry measurement that exceeds the pyloric diameter, the Court finds that even if it did, there is no claim requirement that the dosage form start out at any particular size. There is only the requirement that its swollen size is larger than the pyloric diameter to promote the dosage form remaining in the stomach for the duration of the fed mode.

Consequently, the Court concludes that Plaintiff has established by the preponderance of the evidence that Defendant's 300 mg and 600 mg ANDA products meet the limitations of the "when swollen . . . to promote retention in the stomach during said fed mode" element of Claim 1 of the '280 Patent. As such, given the parties' stipulations as to the other claim elements, the Court finds that Defendant's 300 mg and 600 mg ANDA products will, if produced and marketed, directly infringe Claims 1, 12, 14, and 45 of the '280 Patent

c. The '962 Patent (Oval)

Depomed asserts the '962 Patent against Actavis's 600 mg ANDA product, not its 300 mg ANDA product. There is only one claim element in dispute with respect to the '962 patent: claims 5, 8, 10 and 13 of the '962 Patent all require that the dosage form have "a shape which when projected onto a plane, is either an oval or a parallelogram." As

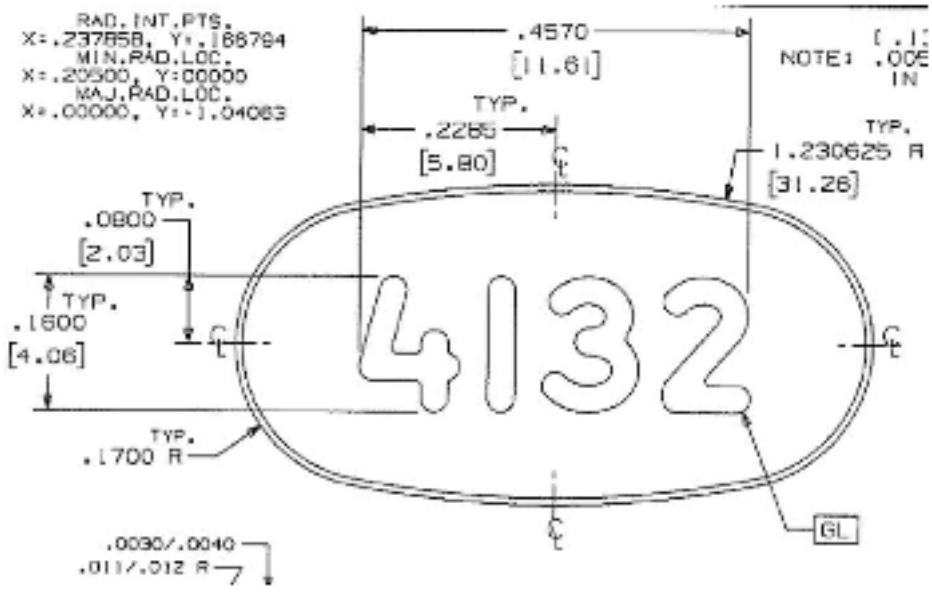
Depomed has not asserted that Actavis's tablet is a parallelogram, the infringement dispute centers on whether the 600 mg ANDA product is an "oval."

The parties have agreed that the term "an oval" is to be construed as "any curve that is closed and concave towards the center wherein the geometric form bounded by the closed curve has a first and second orthogonal axes of unequal length." Stip. Facts ¶ 44. Dr. Hopfenberg explained this construction. He testified that a POSA would understand a "closed" curve as one that goes around and turns back on itself, Tr. 442:1-6., a "concave" curve as a line that is concave toward a center point in, for example, a matrix dosage form, Tr. 442:10-21, and that "first and second orthogonal axes of unequal length" are perpendicular to each other, Tr. 444:7-13. He explains credibly that a POSA would understand an axis as a line of symmetry that divides a two-dimensional shape or object into symmetrical halves. Tr. 443:3-22.

The following is a photograph of the 600 mg ANDA product:

PHYJTX 2.

The drawing for the punches used to make the tablets show the profile for the tablet:



PTX 57.

Dr. Hopfenberg testified that the above diagram of the punch used by Actavis for the 600 mg ANDA tablets shows a closed curve, concave toward the center with a first and second orthogonal axis of unequal lengths (orthogonal axes are designated by the C_L), therefore, it satisfies the agreed construction of "an oval." Tr. 445:22 – 446:7, 450:2-12; PTX000057. Exemplar samples of the 600 mg ANDA product match the shape shown in the punch diagram. PHYJTX 2; PTX 56; PTX 57. Dr. Hopfenberg also concluded that an exemplar sample of the 600 mg ANDA product projects an oval consistent with the agreed construction of "an oval." PHYJTX 2.

Depomed also points out that Actavis on at least one occasion referred to its ANDA product as oval shaped. Actavis formulation scientist, Radi Hejazi, issued a purchase request for 27 tablet dies to be used to manufacture the 600 mg ANDA product. Tr. 78:24 –

79:22, 87:24 – 88:1; 446:15-19; 447:6-16; PTX000043; PTX000044, PTX000057. In the body of the purchase order, Dr. Hejazi described the requisitioned punch as specific-sized "**Oval** Shape Embossed with 4132." Tr. 79:16-18; PTX000044 (emphasis supplied). While certainly far from dispositive, the Court does find the fact that an Actavis employee referred to the 600 mg ANDA product as an "oval" to have some relevance to its inquiry.

Dr. Friend testified in response to Plaintiff's infringement case-in-chief. Contrary to Dr. Hopfenberg's opinion, Dr. Friend, relying on tableting literature, testified that the 600 mg ANDA product is not an oval but is rather a "modified capsule." Tr. 511:12-18. In reaching this conclusion, however, Dr. Friend concedes that he did not apply the parties' agreed-upon claim construction of "oval" because he found it confusing and unclear. Tr. 513:17-20. He further stated that he did not apply the agreed-upon construction because, specifically with respect to the phrase "geometric form bounded by a closed curve," he found it could apply to other tablet shapes as well, specifically almond. Dr. Hopfenberg disputes this. Tr. 480:8 – 482:6, 492:2-9. Dr. Friend also disagrees with Dr. Hopfenberg's definition of the term axis, disagreeing specifically with Dr. Hopfenberg's testimony that symmetrical halves are required for two-dimensional objects.

The Court gives Dr. Friend's testimony regarding infringement of the '962 patent little, if any, weight. As a general matter, based on the Court's consideration of the content of his testimony and the Court's own observation of the witness' demeanor, the Court finds him to be a less credible witness than Dr. Hopfenberg. Thus, where their testimony is at odds, the Court credits Dr. Hopfenberg's testimony over that of Dr. Friend.

Here, the parties stipulated to a claim construction and advised the Court of their agreement. D.I. 188 (Joint Claim Construction and Prehearing Statement). Yet Dr. Friend

(and Defendants) chose to ignore that construction. Indeed, the Court finds no reference to it in Defendant's post trial submission. While they do not expressly offer an alternative construction, Dr. Friend's testimony makes clear that he is substituting the definition of "oval" set forth in the certain tableting literature for the construction agreed to by the parties. In their post-trial submission, Defendants in effect ask the Court to adopt that new construction.

The Local Patent Rules, however, set forth the procedure for parties to follow to resolve claim construction disputes. Following these procedures earlier in this litigation, the parties advised the Court that they had agreed on a construction for "oval." D.I. 188 (Joint Claim Construction and Prehearing Statement). Defendant never advised the Court of any change and never sought to withdraw from that stipulation. Defendants, therefore, are estopped from arguing for a different construction at trial.

Further, to the extent that the Court would be required to construe the term "oval," it would adopt the stipulated construction. Based on Dr. Hopfenberg's testimony, the Court rejects Defendant's contentions that the stipulated construction is at odds with the intrinsic evidence. Furthermore, the stipulated construction is identical to the Court's prior construction of this term in *Depomed, Inc. v. Sun Pharma Global FZE*, 2012 WL 3201962 *15 (D.N.J. 2012), and there has been no credible evidence presented that compels a different construction.

Applying the proper construction within the appropriate analysis, the Court concludes based upon the findings above that the 600 mg ANDA product literally infringes the "wherein said matrix has a shape which when projected onto a plane, is either an oval or a parallelogram" element of claim 1 of the '962 Patent. Actavis has stipulated to

infringement of all other elements of the asserted claims of the '962 Patent. Consequently, the Court finds that the 600 mg ANDA product will, if produced and marketed, directly infringe asserted Claims 5, 8, 10, and 13 of the '962 Patent.

3. Indirect infringement

Claims 18, 25, 26, 34, 61 and 62 of the '927 Patent, claims 6, 7 and 11 of the '756 Patent, claims 17 and 24 of the '332 Patent and claim 22 of the '992 Patent are directed to methods of treatment involving administration of a gastric retained dosage form comprising gabapentin. Plaintiff asserts indirect infringement against Actavis with respect to these claims, specifically, that Actavis contributorily infringes or induces the infringement of these claims.

a. Contributory Infringement

The Court finds that Depomed has shown by the preponderance of the evidence that Actavis will contribute under 35 U.S.C. § 271(c) to the infringement of the asserted method claims of the '927, '756, '332 and '992 patents. As an initial matter, the Court finds that physicians and patients will directly infringe the asserted method claims. The proposed Actavis ANDA label instructs that "Gabapentin is a prescription medicine used in adults 18 years and older to treat pain from damaged nerves, (neuropathic pain) that follows healing of shingles, a painful rash that comes after a herpes zoster infection" which is otherwise known as postherpetic pain, a type of neuropathic pain. PTX000136 at ACTGAB000321131; Tr. 290:1-10. The dosage form will be administered by a health-care professional following the label's method of treating, which is the same as used in the Gralise label. Tr. 285:5-8, 305:6-11. For the reasons stated above, these acts will directly infringe the asserted gabapentin patent claims.

Second, Actavis had knowledge of the patents at issue as evidenced by their submission of a Paragraph IV certification to FDA and notice to Depomed. Stip Facts ¶¶ 15, 16, and 18-22.

Third, the ANDA product may not be marketed for non-infringing uses. Drug companies are not permitted to promote their products for anything other than what is approved in the label. Tr. 288:10–20. The label provided by Actavis indicates that it may be used only for the management of postherpetic neuralgia, which is a form of neuropathic pain and a therapeutic use. Tr. 289:2-10; 289:23 – 290:10; PTX000136 at ACTGAB000321105. Defendant argues that this element of the contributory infringement analysis (*i.e.*, that there are not significant noninfringing uses) has not been met due the existence of a number of off-label uses exist for the ANDA. However, because Actavis cannot expressly market its product for any of these uses, the Court finds this third element to be met.

Fourth, the Actavis 300 and 600 mg dosage forms are a material part of the '927, '756, '332 and '992 Patent method claims because the methods require the administration of gabapentin in a therapeutically effective amount, for the purposes of treating neuropathic pain or postherpetic neuralgia, or diseases responsive to a therapeutic dose of gabapentin. Tr. 283:9–284:13; 285:3–8; 285:18–286:14; 287:15–20. Actavis has stipulated that the ANDA products meet these elements. Stip. Facts¶¶ 5, 9, 11, 13. The asserted method claims of the patents generally require gastric retained dosage forms with single polymer matrices made up of at least one swellable hydrophilic polymer that swells in size and dimensions in an unrestrained manner and release drug by diffusion over at least five hours.

Tr. 284:4-13. Actavis has stipulated that it meets these elements as well. Stip. Facts ¶¶ 5, 9, 11, 13. Thus, the ANDA products factually constitute a material part of the method claims.

All elements of the claim having been met, the Court finds that Actavis will contribute to the infringement of the asserted method claims of the '927, '756, '332 and '992 patents it its ANDA products are produced and marketed.

b. Induced Infringement

Likewise, the Court finds that Defendant will induce infringement of the asserted method claims. First, as discussed above, there will be direct infringement of the asserted claims. Further, Actavis will knowingly and intentionally induce infringement of the '927, '756, '332 and '992 Patents. Actavis had knowledge of the patents at issue as evidenced by their submission of a Paragraph IV certification to FDA. Stip Facts ¶¶ 15, 16, and 18-22. Further, Actavis agrees that the ANDA products meet the relevant elements of the asserted method claims of these patents. Stip. Facts ¶¶ 5, 9, 11, 13. Actavis also agrees that the Gralise tablets are embodiments of the asserted method claims. Tr. 272:12–273:23; PTX000014 at ACTGAB000000336; Stip. Facts ¶¶ 111-116. The ANDA dosage form will be administered by a health-care professional or user following the label's method of treating, which is the same as used in the Gralise label. Tr. 285:5-8, 305:6-11; *see* DTX 31. Both labels instruct the user that the gabapentin tablets are to be "taken orally, once- daily, with the evening meal." PTX 136 at ACTGAB000321105. Gabapentin is approved for the treatment of postherpetic neuralgia. Tr. 883:20-884:9. The label for the ANDA product that it is to be used for the management of postherpetic neuralgia, a form of neuropathic pain and a therapeutic use. Tr. 289:2–10; 289:23 – 290:10; PTX000136 at ACTGAB000321105. *See Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir.

2010) (product label authorizing the patented use was evidence of affirmative intent to induce infringement because it "would inevitably lead some consumers to practice the claimed method").

F. OBVIOUSNESS

1. Burden of Proof

An obviousness analysis starts from the presumption that the challenged patent is valid, as every claim of a duly issued patent is accorded a statutory presumption of validity. *See* 35 U.S.C. § 282. As such, parties challenging the validity of a patent must prove invalidity by clear and convincing evidence. *See id.*; *Microsoft Corp. v. i4i Ltd. Partnership*, 131 S.Ct. 2238, 2243, 180 L.Ed.2d 131 (2011); *Innovative Scuba Concepts, Inc. v. Feder Indus., Inc.*, 26 F.3d 1112, 1115 (Fed. Cir. 1994). Clear and convincing evidence is a higher burden of proof than preponderance of the evidence. *See Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S.Ct. 2433, 81 L.Ed.2d 247 (1984). To be clear and convincing, evidence must "place[ ] in the factfinder 'an abiding conviction that the truth of [the] factual contentions are highly probable.' " *Procter & Gamble Co. v. Teva Pharma. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *id.*)). Clear and convincing evidence should "instantly tilt[ ] the evidentiary scales" in favor of its proponent when weighed against the opposing evidence. *Colorado v. N.M,* 467 U.S. at 310.

2. Applicable Legal Standards

"A patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). "The [obviousness]

analysis is objective" and judged as of the "time the invention was made." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007) (citation omitted).

The ultimate determination of obviousness is a question of law based on underlying factual findings, including the level of ordinary skill in the pertinent art; the scope and content of the prior art; the differences between the claimed invention and the prior art; and objective indicia of nonobviousness, *i.e.*, evidence of factors such as whether the claimed invention is a commercial success, provides unexpected benefits, satisfies a long-felt need, or succeeds where others have failed. *See id.*; *see also Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966) ("[Obviousness] lends itself to several basic factual inquiries. Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined."). While party defending a patent may offer evidence of secondary considerations of nonobviousness, secondary considerations of nonobviousness may not overcome a strong *prima facie* case of obviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

Notably, "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR*, 550 U.S. at 427. Where the issue of obviousness is based on a combination of elements found in the prior art, "the combination must do more than yield a predictable result." *Id.* at 416. In fact, "a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* This is because "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents

combining previously known elements, deprive prior inventions of their value or utility." *Id.* at 419. "In other words, obviousness exists when 'a finite, and in the context of the art, small or easily traversed number of options ... would convince an ordinarily skilled artisan of obviousness.' " *Purdue Pharma Products L.P. v. Par Pharmaceutical, Inc.*, 642 F.Supp.2d 329, 368 (D. Del 2009) (quoting *Ortho–McNeil Pharm., Inc. v. Mylan Labs.*, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

Importantly, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Rather, the party challenging validity must show that a person of ordinary skill in the art "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and ... would have had a reasonable expectation of success in doing so." *Procter & Gamble*, 566 F.3d at 994 (quoting *Pfizer*, 490 F.3d at 1361). The skilled artisan would interpret prior art references "using common sense and appropriate perspective." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011).

The obviousness standard is a somewhat flexible one. The Supreme Court has held that a patent may be obvious in light of the combination of prior art if the combination was "obvious to try." *Id.* at 421. This flexible standard expands the obviousness analysis beyond just "published articles and the explicit content of issued patents." *Id.* at 419. Other forces, including forces such as market demand, may also be examined to determine whether it would be obvious to combine more than one known element. *Id.* In broad terms, "any need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner

claimed." *Id.* at 420. The Federal Circuit has noted that a finding of obviousness "does not require absolute predictability of success ... all that is required is a reasonable expectation of success." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)); *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (same); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[T]he expectation of success need only be reasonable, not absolute" nor "a guarantee.").

In conducting the obviousness analysis, the claimed invention must be viewed in light of the art that existed at the time the invention was made. *See* 35 U.S.C. § 103(a); *Uniroyal*, 837 F.2d at 1050–51. "The term 'prior art' as used in section 103 refers at least to the statutory material named in 35 U.S.C. § 102" that was available to a hypothetical person of skill in the art at the time the invention was made. *Riverwood Int'l Corp. v. R.A. Jones & Co., Inc.*, 324 F.3d 1346, 1354 (Fed. Cir. 2003). "To ascertain the scope of the prior art, a court examines the field of the inventor's endeavor and the particular problem with which the inventor was involved." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir.1998) (citations and internal quotes omitted).

What a reference teaches is a question of fact. *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993). The Court should not "analyze each prior art reference in isolation without considering the prior arts' teaching as a whole in light of the creativity and common sense of a person of ordinary skill." *Duramed Pharms., Inc. v. Watson Labs., Inc.*, 2011 WL 1086573, at *4 (Fed. Cir. Mar.5, 2011). Importantly, the Federal Circuit has admonished against the use of the claimed invention to define the prior art:

> Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness .... By importing the ultimate solution into the problem facing the inventor, the district court adopted an overly narrow view of the scope of the prior art. It also infected the district court's determinations about the content of the prior art.

Monarch Knitting, 139 F.3d at 881 (citations omitted).

All teachings in the prior art must be considered in the obviousness determination, "including that which might lead away from the claimed invention." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed.Cir.1988). "[A] reference must be considered as a whole, including the portions that argue against or teach away from the claimed invention." *Armament Sys. & Procedures, Inc. v. Monadnock Lifetime Prods., Inc.*, 1998 WL 537746, at *8 (Fed. Cir. Aug.7, 1998) (citing *Bausch & Lomb*, 796 F.2d at 448). "Where the prior art contains apparently conflicting teachings (*i.e.*, where some references teach the combination and others teach away from it) each reference must be considered for its power to suggest solutions to an artisan of ordinary skill[,] considering the degree to which one reference might accurately discredit another." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed.Cir.2006) (citation and internal quotes omitted).

Courts are warned against improperly using hindsight in the obviousness analysis. It is impermissible to use "hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Laboratories*, 512 F.3d 1363, 1374 n. 3 (Fed. Cir. 2008); *see also KSR*, 550 U.S. at 421; *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) ("Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the

prior art references and the then-accepted wisdom in the field."), abrogated on other grounds, *In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). "A factfinder should be aware ... of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *KSR*, 550 U.S. at 421.

3. Person of Ordinary Skill in the Art

Defendant's expert Dr. Flanagan defined a person of ordinary skill in the art ("POSA") as "a person with a Ph.D. in chemistry, chemical engineering, pharmaceutical sciences or a related discipline. Alternatively, the person could have a master's degree in one of those fields with at least two years of practical experience and alternatively, the person could have a bachelor's degree in one of those fields with even more practical experience." Tr. 553:17-24.

Plaintiff's expert Dr. Hopfenberg proffered a slightly different definition of a person of ordinary skill in the art: "the person of ordinary skill … would have formal education, at least a bachelor degree in the field of chemistry, chemical engineer, pharmaceutical science and/or material science, the focus on polymer science and having substantial experience in the development of controlled-release drug dosage forms." He further opined that if this person had a Ph.D., then only two years of industry experience would be required. Tr. 932:17-25.

Although under Plaintiff's definition a POSA would have a bit more practical experience, the differences between the two definitions appears to be immaterial. Both experts agree that their opinions would not change if the Court adopted the other's definition of a POSA. Tr. 554:6-555:1; Tr. 933:11-13. Consequently, as resolution of the

differences between the parties' definitions will not affect the outcome of the case, the Court need not resolve them.

4. Gabapentin Patents

Depomed's asserted composition and method claims are directed to a specific type of extended-release gabapentin oral dosage form that releases gabapentin in the stomach over several hours and delivers the drug in such a way that the human achieves certain blood concentrations of the drug and that the gabapentin has a therapeutic effect. JTX 3- 7.

a. Obviousness Contentions

Actavis contends as follows:

• The asserted claims of the '927 Patent would have been obvious to one of ordinary skill over Depomed's WO '107 (DTX 234) in view of Rowbotham (DTX 313), along with the knowledge of a person of ordinary skill in the art as evidenced McLean (DTX 267) and Stevenson (PTX 500).

• The asserted claim of the '989 Patent would have been obvious to one of ordinary skill over WO '107 (DTX 234) in view of Rowbotham (DTX 313), along with the knowledge of a person of ordinary skill in the art as evidenced by McLean (DTX 267) and Stevenson (PTX 500).

• The asserted claims of the '756 Patent would have been obvious to one of ordinary skill over Depomed's WO '107 (DTX 234) in view of Rowbotham (DTX 313), along with the knowledge of a person of ordinary skill in the art as evidenced by McLean (DTX 267) and Stevenson (PTX 500).

• The asserted claims of the '332 Patent and the '992 Patent would have been obvious to one of ordinary skill over WO '107 (DTX 234) or WO '128 (DTX 236) in view of Rowbotham (DTX 313).

b. Priority Dates

There appears to be no dispute as to the relevant dates with respect to the obviousness analysis. The priority date of the Gabapentin Patents ('927, '989, '756, '332 and '992 Patents) is October 25, 2001. *See* JTX003 ('927 Patent) (issued from application no. 10/280,309); JTX004 ('989 Patent) "Related U.S. Application Data" (issued from continuation of application no. 10/280, 309 and claiming priority to provisional application no. 60/335,248 filed October 25, 2001); JTX005 ('756 Patent), "Related U.S. Application Data" (claiming priority to provisional application no. 60/335,248 filed October 25, 2001); JTX006 ('332 Patent), "Related U.S. Application Data" (same); JTX007 ('992 Patent), "Related U.S. Application Data" (same).

c. Prior Art

(i) Gabapentin

Gabapentin was conceived of and synthesized in the early 1970s by Goedecke, A.G., in Germany, which was part of Warner-Lambert at the time. Stip. Facts ¶ 117; Tr. 857:3-9. In December 1993, the FDA approved and Warner-Lambert commercialized an immediate release formulation of gabapentin. Stip. Facts ¶ 119; Tr. 686:1-5. Neurontin is the trade name of this immediate release formulation, and its recommended dosing schedule is three times per day. Tr. 731:19-20; 751:3-5.

When Neurontin was first approved in the United States, it was indicated "as adjunctive therapy in the treatment of partial seizures with and without secondary

generalization in patients over 12 years of age with epilepsy. Neurontin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 - 12 years." DTX 291 at GRALISE_JDG_00000158.

In the 1990's the use of gabapentin grew beyond the treatment of epilepsy and was prescribed off label for other purposes. Tr. 672:22-24. The Rowbotham reference, published in 1998, concluded that Neurontin was effective for the treatment of neuropathic pain, such as postherpetic neuralgia. DTX 313 (Michael Rowbotham et al., *Gabapentin for the treatment of Postherpetic Neuralgia: A Randomized Controlled Trial*, 280 J. AM. MED. ASS'N 1837, 1837-42 (1998); Tr. 559:4-560:5; 857:3-8. As a result of its off label uses, Neurontin eventually became a blockbuster drug product by the late 1990s. Tr. 772:6-11; 975:25 – 976:4; 1067:24 – 1068:14.

Gabapentin has a number of properties that would need to be considered with respect to the development of a controlled-release formulation:

• Absorption

The evidence shows that a POSA in the late 1990's/early 2000 seeking to create an extended-release gabapentin formulation would have had to account for several unique characteristics of the drug. The first was to ensure that the drug was available for absorption. Tr. 964:10-25. Gabapentin was known in the prior art to have some unique absorption properties that would impact the development in a controlled-release formulation. Gabapentin was known to be highly water soluble. Tr. 558:5-559:3; DTX 267 at GRALISE_JDG_ 00000126; Tr. 703:19-24; DTX 291 at GRALISE_JDG_ 00000152; Tr. 263:16-17. It was also known to have a narrow window of absorption in the upper gastrointestinal tract (that is, it is absorbed only in the upper region of the small

intestinal tract) and to be absorbed via a saturable transporter. Tr. 560:6-561:9, 564:22-565:1; PTX 500 at GRALISE_JDG_ 00000601, GRALISE_JDG_00000603; DTX 267; 711:18-22 (testimony that McLean states that gabapentin "is transported across the gut wall by the L system amino acid transporter," and that the "[a]bsolute bioavailability of gabapentin is dose-dependent, probably as a result of the saturable absorption by the L system amino acid transporter."). Thus, to develop a controlled release formulation, a POSA would have needed to account for gabapentin's unique absorption properties formulation. According to Plaintiff, gabapentin's absorption properties created substantial challenges to the development of a controlled-release formulation. Tr. 964:2-8. Defendant, on the other hand, contends that a POSA would have known that these properties made gabapentin ideal for a gastric-retained controlled-release dosage form. Tr. 637:2-6; 964:15-965:16; *see* DTX 234.

There is no dispute that gabapentin has a narrow window of absorption. Tr. 560:6-8; 983:12-17; 828:16 – 829:5. Defendant's expert Dr. Flanagan testified that the window of absorption was an important characteristic for a formulator developing a controlled-release dosage form. Dr. Flanagan testified that "[i]f the drug is only absorbed in a certain region of the GI tract, then one has to develop a formulation that will release it in the region where it will be absorbed." Tr. 564:13-17; *see also* Tr. 964:15-17 (Dr. Felton: "[B]ecause the drug is absorbed in the upper regions of the small intestine, the drug would need to be released at that site in order to be absorbed into the body.")

Pre-clinical studies in dogs by Stevenson show that gabapentin absorption takes place in the small intestines but largely does not occur in the large intestines. Tr. 339:11-16; PTX 500 at Gralise_JDG_00000602. Stevenson states "[c]omparison of the blood-level

data from oral and jejunal administration of gabapentin indicates that there is substantial absorption from the duodenum and upper jejunum. Most important, gabapentin plasma levels from colonic administration are substantially lower than those obtained from oral and upper intestinal administration." Tr. 339:17 – 340:2; PTX000500 at Gralise_JDG_00000602.

The poor absorption of gabapentin and its restricted area of absorption posed certain challenges to designing an effective controlled-release formulation. As noted by one reference in 2000:

> Gabapentin has a half-life of 5 to 7 hours and requires an administration interval of 8 hours; however, it is absorbed by an L- amino acid carrier system that may not be present throughout the gastrointestinal tract and which may be saturable. These characteristics would limit the use of an ER formulation.

PTX 501; Collins *et al.* (2000) at 205 (citation omitted).); *see also* Tr. 853:8-16.

Similarly, other literature noted:

> To date, efforts to develop a sustained release formulation of gabapentin have failed, primarily due to the lack of significant absorption of the drug in the large intestine (Kriel et al., 1997).

Cundy *et al.* (2004) PTX000269 at 316.

With gabapentin being absorbed in the upper regions of the gastrointestinal tract, the drug would need to be released at that site or above in order to be absorbed into the body. Plaintiff's expert Dr. Felton stated that, as a result, "[t]here are potentially two general approaches to achieve that drug release in the right location in the body. The first would have been to slow intestinal motility of the dosage form in the small intestines." Tr. 964:18-25. However, that would require additional medication to achieve and Dr. Felton opined that "it is probably not a good idea to have to take one medication in order to get a

second medication absorbed." Tr. 964:24-25. The second alternative was to deliver the drug by way of one of the several available gastro-retentive systems. Tr. 964:10 – 965:17, 967:21 – 969:8. *See also* PTX 274 (Davis 2005) ("Methods designed to provide longer contact of the drug or delivery system with the crucial absorption region fall into two different categories: (i) those that attempt to slow down transit through the small intestine; and (ii) those that attempt to hold the drug formulation above the absorption window through gastric retention.")

• Pharmacokinetics and Bioavailability

As noted above, gabapentin is absorbed in the upper gastrointestinal tract by saturable transporters. Tr. 748:20 – 749:3; 563:8-16. It was reported for the first time in 1995 that gabapentin was saturably absorbed by L-amino acid type transporters. Tr. 747:9 – 748:7; PTX000271. Thus, a second challenge faced in developing an extended-release formulation of gabapentin would have been pharmacokinetics and bioavailability, that is, ensuring that the drug release occurs at a rate that will be not saturate the saturable absorption system but yet is high enough to get therapeutically meaningful blood levels. Tr. 563:8-16. "Saturable absorption" means that the transporters can only bring in a certain amount of drug at any given time. Tr. 563:19- 24; Tr. 710:11-17. Consequently, if more than that amount of drug reaches the transporter, then the additional amount of drug simply will not be absorbed. Tr. 563:19-24; 710:11-17.

Gabapentin's short half life also was potentially problematic to the development of an extended-release formulation. Gabapentin's half-life of about 6 hours meant that if a single dose per day was administered, absorption would need to be maintained over an

extended period of time as the half-life in the blood would be short. Effectively, after 10-12 hours with no absorption, 75% of gabapentin would be eliminated. Tr. 759:4-7, 758:7-13.

• Degradation

Another challenge facing a POSA seeking to develop an extended-release gabapentin dosage form is that in the acidic environment of the stomach gabapentin degrades into lactam, which can be toxic. Tr. 855:7-13. Gabapentin degrades slowly into lactam as a function of pH, temperature and buffers which can accelerate some of this process. Tr. 856:1-3; PTX000290. As in the case of any drug that degrades in an acidic environment such as in the stomach, as the drug degrades there will be less drug that could be absorbed for its therapeutic effect.

Defendant takes the position that degradation into lactam is a challenge that has already been overcome. On cross examination, Plaintiff's expert Dr. Gidal admitted that Warner-Lambert had previously discovered "that gabapentin can convert into lactam," and that Warner-Lambert "solved the problem and got a patent on that solution." Tr. 858:12-18. However, Defendant failed to offer to any further evidence as to what that "solution" is, under what circumstances it is employed, and whether and to what extent it may apply in the context of the development of an extended release gabapentin formulation. The Court, therefore, cannot conclude that the existence of this "solution" negates from consideration by a POSA the challenge of avoiding the degradation of gabapentin into lactam in the development of a controlled-release gabapentin formulation.

• Blockage

In addition to lactam formation, evidence shows that another safety challenge with a gastro-rententive system is avoidance of potential blockages. Because such a formulation is

designed to stay in the stomach for an extended period, a formulator must consider the risk the dosage form can get lodged in the digestive tract. Tr. 966:12-19. For example, the 2005 *Davis* reference notes that the gastric retentive system must be retained in a safe and reliable manner: "It must not swell or expand in the esophagus or in the intestines, if it emptied prematurely from the stomach (*e.g.* problems could arise from the formation of an insoluble mass known as bezoar)." PTX274 at DEPOACT0970226.

• Therapeutic Effectiveness

Yet another consideration is ensuring that a therapeutically effective amount of the drug gets to the target site in order to exert its therapeutic effect. Tr. 966:20 – 967:1.

Therapeutically effective dosages for gabapentin in an immediate release formulation (Neurontin) were known in the prior art. Daily doses ranging from 300 mg/day to 3,600 mg/day of gabapentin were known to be an effective treatment of neuropathic pain. Tr. 559:4-560:5; Tr. 619:11-14, 622:17-623:3; DTX 313 at GRALISE_JDG_00000452 (Study participants "began with an initial dose of 300 mg/d" which was then "increased over the next four weeks (titration period) in a step-up manner (900, 1800, 2400, and 3600 mg/d divided three times a day), to a maximum total dose of 3600 mg/d."), GRALISE_JDG_00000451 ("Conclusions—Gabapentin is effective in the treatment of pain and sleep interference associated with [postherpetic neuralgia]."))

> With respect to the treatment of epilepsy, the Neurontin label states that an
>
> effective dose of Neurontin® is 900 to 1800 mg/day and given in divided doses (three times a day) using 300 or 400 mg capsules, or 600 or 800 mg tablets. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 or 400 mg capsules, or 600 or 800 mg tablets three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also

> been administered to a small number of patients for a relatively short duration, and have been well tolerated.

Tr. 620:15-24; DTX 291 at GRALISE_JDG_00000169.

However, as Dr. Gidal testified, information about the therapeutic efficacy of the immediate-release formulation Neurontin does not necessarily translate to an extended release formulation. Tr. 842:21-843:15. According to Dr. Gidal, this is due to the saturable absorption seen with gabapentin, which is more unpredictable than linear absorption, as well the inter-person variability and even the effect of food on the absorption of gabapentin. Tr. 817:8-818:1.

(ii) Gastric Retained Dosage Forms Generally

According to Defendant's expert Dr. Flanagan, there were no FDA approved gastric retained dosage forms available in the market in 2001. Tr. 663:8-12. In fact, the weight of the credible evidence shows that in the late 1990's and early 2000's, the gastro-retentive drug delivery system was an emerging art and was not well-developed. Tr. 968:15-21.

The *Hwang* reference provides a comprehensive view of the state of the art as of 1998. *See* DTX 22, Sung-Joo Hwang, et al., *Gastric Retentive Drug-Delivery Systems*, Critical Reviews, 15 CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYS. 243, 243–84 (1998). In 1998, no long-term gastric retention device was available, and a need for such a device was expressed in the *Hwang* paper. Tr. DTX 222; Tr. 948:3-17. The *Hwang* reference describes several possible approaches to gastro-retentive drug delivery system, Tr. 656:9-11, which include: (1) gas generating floating systems; (2) low density core systems; (3) high density systems; (4) mucoadhesive systems; (5) magnetic systems; (6) unfoldable, extendible or expandable systems, including systems extending to

complex geometric shapes and larger sizes; and (7) superporous hydrogel systems. DTX 222, GRALISE_JDG_00000396-415; Tr. 661:13-662:9.

Hwang concludes that it is unclear at that time whether any gastric retention device is "truly working or not" and "[w]e have great hope that a long-term gastric retention device for human application will be developed in the near future." DTX 222, GRALISE_JDG_ 00000417, GRALISE_JDG_00000418; Tr. 948:3-17. The concluding section of this reference, under the heading of "Optimization of Gastric Retention Devices for Human Applications", states:

> The literature is full of conflicting information. Gastric retention devices that work in one laboratory often prove not to work in others. When a proposed gastric retention device doe[s] not work, the immediate conclusion drawn by the study is obviously that the system does not work. As we reviewed the literature, we have noticed a few things. First of all, no study has been done comprehensively to conclude whether any gastric retention device is truly working or not. Most of the studies that showed that a proposed system did not work were often based on inadequate controls and an inadequate number of volunteers. While the studies may have produced negative results, these results were hardly sufficient to conclude that the system did not work.
>
> * * *
>
> "The lesson here is that there's too much variation in human volunteers, unrealistic to derive any conclusion from advanced retention study involving only a handful of human volunteers."
>
> * * *
>
> We have great hope that a long-term gastric retention device for human application will be developed in the near future. As presented here, each gastric retention system approach has its own unique concept and each requires further improvements to be effective. Progress will only be possible if all the researchers in the field work together to analyze a concept, test it, and find ways to overcome limitations. Only after we accomplish long-term gastric retention devices can the full benefits of controlled-release technologies be realized for oral controlled-release dosage forms.

DTX 222 at GRALISE_JDG_0000417-18.

(iii) International Patent Publication No. WO 98/55107

International Patent Publication No. WO 98/55107 A1 ("WO '107"), which was authored by Depomed employees and published December 10, 1998, is titled "Gastric-Retentive Oral Drug Dosage Forms for Controlled Release of Highly Soluble Drugs." DTX 234 at GRALISE_JDG_00000841. The abstract for WO '107 states that the purpose of the described dosage form is as follows:

> Drugs that are freely or highly soluble in water are formulated as unit dosage forms by incorporating them into polymeric matrices comprised of high molecular weight hydrophilic polymers that swell upon imbibition of water. The dosage form can be a single compressed tablet[]. . . . The oral formulation is designed for gastric retention and controlled delivery of an incorporated drug into the gastric cavity, and thus administered, the drug is released from the matrix into the gastric fluid by solution diffusion. The swollen polymeric matrix, having achieved sufficient size, remains in the gastric cavity for several hours if administered while the patient is in the fed mode, and remains intact long enough for substantially all of the drug to be released before substantial erosion of the matrix occurs . . . .

Tr. 556:22-557:8; DTX 234 at GRALISE_JDG_00000841.

As described by Dr. Flanagan, the WO '107 discloses

> a drug being dispersed in a polymeric matrix and that matrix is water swellable. The drug is released based on diffusion that can be slowed by altering formulation characteristics. The polymers in the matrix swell upon ingestion and that promotes gastric retention during the fed mode. The swelling is also in a dimensionally-unrestricted manner and soluble drugs can be absorbed -- they're absorbed mostly in the stomach or high in the gastrointestinal tract -- such as Metformin can be incorporated into the formulations that are disclosed and that the said dosage form comprises a solid polymeric matrix in which the drug is dispersed.

Tr. 556:20 - 557:8.

In particular, WO '107 discusses gastro-retentive systems "to treat local conditions in the stomach as well as to provide control release for drugs that are absorbed from a narrow window of absorption." Tr. 973:8-974:3. In vitro release examples that are cited in

WO '107 are Metformin hydrochloride, Captopril and Vancomycin." Tr. 973:22-24. Gabapentin is not expressly cited as a possible drug to be used in WO '107 dosage form.

(iv) International Patent Publication No. WO 99/47128

International Patent Publication No. WO 99/47128 A1 ("WO '128"), entitled *Biphasic Controlled Release Delivery System for High Solubility Pharmaceuticals and Method*, was published on September 23, 1999. DTX 236 at GRALISE_JDG_00000055. Dr. Mayersohn explained that WO '128 is directed to "a new dosage form for highly water soluble medicaments, such as the antidiabetic metformin, which provides for extended release of the drug and prolonged gastric residence which enables efficient delivery of drugs normally absorbed in the upper gastrointestinal tract, and to a method for preparing such dosage form." Tr. 698:8-14; DTX 236 at GRALISE_JDG_00000057. The WO '128 application deals with one specific drug, Metformin, Tr. 698:17-18, but lists a number of "high water soluable drugs" and types of "water-soluable drugs" that can be included in the described formulations. GRALISE_JDG_00000079-82. It does not disclose gabapentin or a dosage form containing gabapentin. Tr. 726:1-3; 975:16-24; 1038:24-25.

(v) Rowbotham

In December of 1998, an article by Michael Rowbotham was published in the Journal of the Medical Association entitled *Gabapentin For the Treatment of Postherpetic Neuralgia*. Rowbotham *et al.*, Gabapentin for the treatment of Postherpetic Neuralgia: A Randomized Controlled Trial, 280 J. AM. MED. ASS'N 1837, 1837-42 (1998). Rowbotham concluded that gabapentin was an effective treatment of neuropathic pain, with daily doses ranging from 300 mg/day to 3,600 mg/day. Tr. 559:4-560:5; DTX 313 at GRALISE_JDG_00000452 (Study participants "began with an initial dose of 300 mg/d"

which was then "increased over the next four weeks (titration period) in a step-up manner (900, 1800, 2400, and 3600 mg/d divided three times a day), to a maximum total dose of 3600 mg/d."), GRALISE_JDG_ 00000451 ("Conclusions—Gabapentin is effective in the treatment of pain and sleep interference associated with [postherpetic neuralgia].").) This reference discusses immediate release gabapentin only.

(vi) Comparison of the Inventions and Prior Art

Defendant presented expert testimony explaining that the prior art as discloses or suggests most of the limitations of the asserted claims. Much of this testimony is undisputed, thus, as Defendant's counsel indicated in his opening statement, the key issues to be decided as related to obviousness center on motivation to combine the prior art references and whether there would have been a reasonable likelihood of success in doing so. The Court sets forth below, however, certain limitations from the asserted claims not disclosed in the prior art:

• No reference discloses gabapentin from an extended-release dosage form with bioavailability that is at least 80% as that from an immediate release dosage form. All asserted claims of the '989, '756, '332 and '992 Patents require bioavailability at least 80% as that from an immediate release form. Claim 10 of the '989 Patent, claims 1, 2, 5-7, 11 of the '756 Patent, claims 1, 6, 17, 22, 24 of the '332 Patent and claims 1, 5, 22 of the '992 Patent are asserted in this case. None references relied upon disclose this limitation. Tr. 1031:3-10; Tr. 576:8-13; 997:13 – 998:4; 1038:24 – 1039:3.

• No reference teaches gabapentin from an extended-release dosage form with lower Cmax than that from an immediate release dosage form. Asserted claims 1, 2, 5-7, 11 of the '756 Patent, 1, 6, 17 of the '332 Patent and 1, 5 of the '992 Patent require that the

controlled-release gabapentin dosage form achieve in vivo a lower Cmax than the immediate release gabapentin dosage form. The WO'107 reference does not specifically state that its formulation achieved lower Cmax of any drug compared to that from an immediate release dosage form. Tr. 1037:8-17; 614:19-21.

• No reference teaches gabapentin from an extended-release dosage form with longer Tmax than that from an immediate release dosage form. The WO '107 reference does not specifically state that its formulation achieved longer Tmax of a drug compared to that from an immediate release dosage form. Tr. 1038:1-8. The WO '128 reference does not specifically state that its formulation would result in gabapentin with longer Tmax compared to that from an immediate release dosage form. Tr. 1038:24 – 1039:3. Other references relied upon also does not teach pharmacokinetic parameters from a gastric retained dosage form or from a gabapentin dosage form. Tr. 998:5-22.

• No reference teaches that "at least 40 wt% of the gabapentin is retained in the dosage form one hour after administration." Asserted claims 18, 25, 26, 34, 61, 62 of the '927 Patent, claim 10 of the '989 Patent and claims 1, 2, 5-7, 11 of the '756 Patent contain this limitation. The WO '107 reference does not refer to gabapentin, and has no in vivo data to show that one hour after administration gabapentin is retained at least 40% wt after administration. Tr. 994:21 – 995:10; 996-22 – 997:12.

• No reference teach "the dosage form provides administration of at least 85 wt% of the gabapentin to be delivered over a period of about 5-12 hours." Claim 26 of the '927 Patent requires that the controlled-release gabapentin dosage from that 85% be delivered over a period of about 5-12 hours. It is undisputed that there is no in vivo data presented in the WO '107 reference. Tr. 996:6-21.

c. Motivation

(i) Motivation - Generally

As Actavis argues, evidence at trial showed that one of ordinary skill in the art in 2001 would have had a general motivation to make a controlled release gabapentin formulation to alleviate the burden on patients to take multiple doses per day, improve patient compliance, and reduce the incidence of side effects. Tr. 751:11-18 (Bockbrader: reduce frequency, improve compliance); Tr. 963:21-964:1 (Felton: reduce frequency, improve compliance, lessen side effects) Tr. 558:5-559:3 (Flanagan: reduce frequency, improve compliance); Tr. 873:12-22 (Brown: experiences compliance issues with thrice daily dosing); DTX 267 at GRALISE_JDG_ 00000130 (short half life and resulting three-times per day dosing may result in compliance problems).

However, despite the potential advantages identified with respect to a controlled-release gabapentin formulation, Depomed argues that "no specific motivation existed to make an effective extended-release gabapentin dosage form" because of the challenges that existed to creating such a dosage form. The Court agrees that there is evidence of challenges that may have dissuaded a POSA from believing an effective controlled release formulation of gabapentin could be developed. First, Depomed points to a study by Dr. Gidal published in 1998 that concluded that slower delivery of gabapentin to overcome its saturation problem did not work at a lower dose as the researchers had anticipated. *See* PTX 502 at 91-92 (Gidal *et al*, *Gabapentin Bioavailability: Effect of Dose and Frequency of Administration in Adult Patients With Epilepsy*, EPILEPSY RESEARCH 31 (1998)).

With a drug like gabapentin that is saturable, there would ostensibly be a motivation to create a controlled-release dosage form because such a dosage form would not deliver

the entire dose immediately but rather over a period of time, therefore lessening the problem of saturation. Tr. 364:10-15; 1010:8-12. Gabapentin being absorbed by a saturable mechanism, Dr. Gidal and his team hypothesized that if they gave the same daily dose of the drug but administered it more frequently to simulate a slowly releasing controlled-release dosage form, the bioavailability of drug would improve and more of the drug would get absorbed. Tr. 819:15 – 820:6. However, Dr. Gidal's studies showed, unexpectedly, that although bioavailability improved with patients who were given a 4800 mg/day dose of gabapentin, it did not with a 3600 mg/day dose of gabapentin. Tr. 820:7 – 822:10. Thus, Depomed contends that a POSA would have been skeptical that an extended-release dosage form could avoid saturation.

Second, Depomed points to the fact that the stomach environment was thought to accelerate the degradation of gabapentin into lactam. According to *Hwang*, "drugs unstable in the acidic pH of the stomach cannot be used in gastric retentive devices." DTX 222 at GRALISE_JDG_ 00000387. As noted earlier, "[g]abapentin is a drug that was known to degrade in the presence of acid more quickly to a toxic lactam." Tr. 971:22 – 972:19. Dr. Felton testified that based on this that a POSA would conclude that, as a result, it would "not be a good idea" to put gabapentin in a gastric retained delivery system. Tr. 972:20 – 973:3. Dr. Felton further explained that there were other references also demonstrating "that the drug does degrade to a lactam, a toxic component, and the rate at which that degradation happens is going to be dependent on what people have consumed or what's is in their stomach, whether there's buffer, what the pH is." Tr. 998:24 – 1001:3.

In response to the express concerns about degradation, Actavis refers to International Patent Publication No. WO 93/18755 ("WO '755), entitled Aykly-Substituted

Cellulose-Based Sustained-Release Oral Dosage Forms that was published in 1993. This reference states that its disclosed dosage forms can protect acid- labile peptides, proteins, or proton pump inhibitors from gastric fluid. DTX 230 at GRALISE_JDG_00000902 – GRALISE_JDG_ 00000903. The WO '755 reference teaches drug/polymer mixtures in the form of a "plurality of particles" that are delivered to the stomach in a "tablet or capsule [which] rapidly disintegrates in the gastric fluid to permit the particles to disperse in the stomach. DTX 230 at GRALISE_JDG_ 00000900 and GRALISE_JDG_00000905. There is no evidence, however, that a person of ordinary skill in the art would look to WO '755 for teaching on how to protect gabapentin from the acidic environment of the stomach because this reference contemplates very different release-controlling mechanisms as compared to the Gabapentin Patents. In contrast to the inventions of the Gabapentin Patents, which require the use of the highly soluble drug gabapentin, WO '755 is directed to the formulation of dosage forms for drugs with "limited solubility." DTX 230 at GRALISE_JDG_00000901. Further, the release of these low solubility drugs from a matrix is controlled by their rate of dissolution, while the Gabapentin Patents release drug primarily by diffusion. DTX 230 at GRALISE_JDG_ 00000905; JTX003 12:48-49; *see also* Tr. 264:8 – 265:19.

Also supporting Depomed's argument that no specific motivation existed to make an extended-release gabapentin dosage form is a concern that would have existed as to a dosage form that is dependent on food, because food has a variable effect on gabapentin absorption. Studies have indicated that food has a variable effect on gabapentin absorption. In one study, it was hypothesized that, in the presence of a protein rich diet, gabapentin absorption would be reduced because the amino acids in the protein would compete with

gabapentin for transport since both gabapentin and certain amino acids are transported by the same transporter, *i.e.*, "System L." Tr. 829:21-831:8. Contrary to expectations, the study showed that the presence of a protein rich diet enhanced the bioavailability of gabapentin. Tr. 831:8-24; PTX 276 at DEPOACT0970241 (Gidal et al., *Effect of a High-Protein Meal on Gabapentin Pharmacokinetics*, 23 EPILEPSY RESEARCH 71, 74 (1996))

In another study, Dr. Gidal evaluated gabapentin absorption following a diet of Neurontin mixed with water, apple sauce, orange juice or chocolate pudding. Tr. 832:18 – 834:8; PTX000270 at DEPOACT0958992 (Gidal et al., *Gabapentin Absorption: Effect of Mixing with Foods of Varying Macronutrient Composition*, 32 THE ANNALS OF PHARMACOTHERAPY 405 (1998). The data from this study suggested that food composition, particularly protein, could influence gabapentin absorption.

Dr. Gidal testified that he would have been skeptical of the ability to create an effective controlled-release dosage form of gabapentin because of, among other things, the effect of food on absorption. Tr. 834:19 – 835:20. Dr. Felton similarly noted that the variable effect of food on absorption was a factor that would lead a POSA to believe that gabapentin would not be suitable for use in a gastric-retained dosage form dependent on the presence of food in the stomach. 967:4-10.

In a book chapter that reflect his opinions in 2000-2001, Tr. 738:5-14, 738:25 – 740:11, Actavis expert Dr. Mayersohn discussed the then-state of the art thinking about how food impacts drug absorption. Tr. 737:7-15, 738:5 – 740:11. He wrote the following in regard to food effects on drug absorption:

> Several recent publications have reviewed the effects of food on drug absorption in humans [70-72]. The effect of food on the gastrointestinal absorption of drugs is complex and multidimensional. We are only now

> beginning to understand this complexity. The physical presence of food in the GIT may play a significant role-in affecting the efficient absorption of a drug from an oral dosage form. The ultimate effect of food on the rate and/or extent of gastrointestinal absorption is a function of numerous interacting variables. While some general rules may be postulated, the effect of food on a given drug and its dosage form will require, in general, individual investigation. The U.S. Food and Drug Administration (FDA) has recognized this complexity and requires that all dosage forms that do not immediately release drug (e.g., controlled-release formulations) undergo a food-effects study in humans, for which a "Guidance" has been written (these are available on the FDA webpage-fda.gov).

PTX000521 at DEPOACT0982013; Tr. 738:15 – 739:22. He further noted that there were variables that a POSA must consider with respect to how food effects absorption including "physical chemical characteristics of the drug (e.g., aqueous solubility, oil/water partition coefficient, and stability in gut fluids), the dose of drug, the characteristics of the dosage form, time of drug administration relative to food ingestion, amount of food, and type of food." PTX 521 at DEPOACT0982013; Tr. 739:23 – 740:11

In response to evidence and argument regarding absorption variability based upon food, Actavis provides little more in the way of evidence than the Neurontin label, awareness of which was acknowledged by Depomed's witnesses on cross examination, which states that Neurontin can be taken with or without food. DTX 291 at GRALISE_JDG_00000169. Defendant's implication is that absorption variability based upon food is clinically insignificant. While this is reasonable to infer with respect to the immediate release formulation of gabapentin, there has been no credible evidence presented to indicate the same would be true for an extended-release formulation that releases the drug in incremental amounts over a period of time. The dosage forms of WO '107 and WO '128, for example, must be taken with food, and it is possible that a POSA would try to minimize the food effect by looking for a dosage form that was not dependent on food.

(ii) Motivation - WO '107

As already stated, by October 2001, it was known in the art that gabapentin is highly water soluble and absorbed high in the gastrointestinal tract through a saturable carrier-mediated system. Tr. 686:1-5, 702:4-7; 845:24; 963:2-6; DTX 267 at GRALISE_JDG_ 00000126-28. Given these properties of the drug, a POSA would know that a conventional controlled release dosage form that releases drug along the entire length of the gastrointestinal tract would be inappropriate for gabapentin. Tr. 637:2-6, 702:4-16, 713:22-714:17, 769:24-770:3. Instead, as Dr. Felton explained, a gastric retentive system was the better of the potential approaches to make a controlled release form of gabapentin because it would keep the gabapentin in a place above its window of absorption for an extended period of time. Tr. 964:15-965:16. Named inventor, Dr. Hou, confirmed that it was these known absorption characteristics that made gabapentin a good candidate for a gastric retained, controlled-release dosage form. Tr. 548:11-14. Dr. Hou stated that non-gastric retained dosage forms were not considered for gabapentin. Tr. 548:15-17.

The WO '107 describes a gastric retained dosage form. As stated in the Summary of the Invention in WO '107:

> The invention . . . provides enhanced absorption of soluble drugs that are absorbed mostly in the stomach or high in the gastrointestinal tract, such as metformin hydrochloride or ciprofloxacin. The invention is also useful in providing a multi-hour flow of a drug past the upper part of the small intestine (the most efficient absorption site for many agents).

DTX 234 at GRALISE_JDG_00000845. Dr. Flanagan stated that one of ordinary skill in the art would consider WO '107 dosage form a suitable one for gabapentin because gabapentin is similarly absorbed primarily high in the gastrointestinal tract and is water soluble. Tr. 557:9-25. Dr. Flanagan also opined that one of ordinary skill in the art would

also have had a motivation to replace metformin in the gastric retained formulations disclosed in Depomed's WO '107 with gabapentin because both drugs were known to exhibit saturable absorption high in the gastrointestinal tract. Tr. 564:22-565:1.

However, the evidence shows that there are a number of reasons that a POSA would not necessarily be motivated to combine WO '107 with the identified references to produce the inventions recited in the asserted claims of the Gabapentin Patents. First, as Depomed notes, each asserted claims of the Gabapentin Patents either expressly recites one or more pharmacokinetic parameter (such as AUC, Cmax or Tmax) or it recites therapeutically effective gabapentin (or sometime both). JTX003, JTX004, JTX005, JTX006, JTX007. The WO '107 reference does not disclose any pharmacokinetic element of gabapentin or any drug or any therapeutic administration of a drug. Tr. 974:4-15; 842:7-17; 656:1-3. Without such data, there is insufficient information to know that gabapentin would in fact be absorbed into the blood stream with the appropriate kinetics such that its bioavailability will be at least 80% as that of an immediate release dosage form or with lower Cmax or longer Tmax and, as such, a POSA would be less inclined to use gabapentin in the WO '107 dosage form. Tr. 1031:17 – 1032:5; 1037:19- 25; 1038:9-17.

In this regard, Depomed also points to the fact that WO '107 provides in vitro dissolution curves for drugs like vancomycin which were known to be poorly absorbed orally and would be a poor candidate for therapeutically effective dosage form. Tr. 1015:14- 24; 1059:4-13. Consequently, a POSA would understand that the WO '107 reference teaches a dosage form and not that the drug used in the WO '107 dosage form would necessarily be absorbed into the blood to result in certain pharmacokinetic parameters or that the drug would be therapeutically effective. Tr. 1059:17-23.

Depomed also argues that a "having a general goal of at least 80% AUC, lower Cmax and higher Tmax of gabapentin from a controlled-release versus immediate-release dosage form is insufficient clear motivation to combine when none of the references teach that gabapentin from a controlled-release dosage would be absorbed in blood." D.I. 361 at 135. Defendant's expert Dr. Flanagan testified that all controlled-release formulations are designed to meet the claim limitations of without loss in bioavailability (AUC) or lower Cmax. Tr. 608:14 – 609:10. Dr. Flanagan further testified that without loss in AUC and lower Cmax are the natural consequences of controlled-release dosages. Tr. 609:14 – 610:1. Depomed's expert Dr. Derendorf, however, disagreed with Dr. Flanagan. (Notably, Dr. Derendorf is an expert in pharmacokinetics; Dr. Flanagan is not.) Dr. Derendorf explained that controlled-release formulations can be of many types with different targets, typically the relevant pharmacokinetic profile being one that would be therapeutically effective. According to Dr. Derendorf, such a profile may have a lower Cmax, but that is not always true. Tr. 1032:21 – 1033:9. If the controlled-release product is below minimum effective concentration, the controlled-release product even though it meets all the pharmacokinetic goals, nonetheless would be therapeutically ineffective. Tr. 1034:22 – 1035:18. According to Dr. Derendorf, the minimum effective concentration for gabapentin is not known; therefore, simply by looking at a dose concentration profile, one would not know whether the drug is therapeutically effective or not. Tr. 1035:5-18. The Court finds Dr. Derendorf's testimony persuasive.

Next Depomed argues that no specific motivation existed to put gabapentin in the WO '107 dosage form. Dr. Felton testified a POSA in October 2001 would not select gabapentin for use in the dosage form disclosed in WO '107 because:

- Gabapentin is not mentioned in the WO '107 reference; Tr. 987-988;

- Gabapentin was known to be sensitive to degradation in acidic pH and the dosage form is designed to reside in the stomach for several hours, *id.*;

- The WO '107 reference "focuses quite a bit on a treatment for local effect in the stomach" and gabapentin is not used for such purpose *id.*;

- Gabapentin's "absorption is influenced by the presence of food and the '107 patent application requires the drug product to be administered with food", *id.*;

- One of skill in the art would also not choose gabapentin based on the disclosure of metformin in the WO '107 reference—according to Dr. Felton they are distinct chemical entities with different chemical properties and cannot simply be substituted, *id.*;

- One skilled in the art would not try to develop an extended- release dosage of gabapentin without knowing if release rate of the drug from the dosage form was appropriate. As stated by Dr. Felton, "Without understanding the saturable kinetics, one of skill in the art would not know how quickly the drug needs to come out of that system or for that matter, what blood levels are necessary to achieve a therapeutic effect." Tr. 987-992.

Significantly, gabapentin was not identified in WO '107 reference as a potential drug to use in the '107 dosage form, even though well-known Neurontin was a billion dollar a year drug. Tr. 672:22-673:9. Further, the WO '107 reference states that the formulation is designed for gastric retention, but there is no evidence that the dosage forms "would be gastrically retained in vivo" for several hours. "There is no in vivo data that's presented, there is no swelling data that's presented and to be fair, at the time this was an emerging art and one of skill would look at these systems rather skeptically and would want

to see some evidence that these systems are actually gastric retained." Tr. 1012:6-23; 1024:10 – 1025:4.

Also with respect to motivation, Depomed contends that International Patent Publication No. WO 01/37812 ("WO '812") teaches away from a matrix dosage form being retained in the stomach without an attached membrane. The '812 application is a combination system, comprising at least two components, the matrix and a membrane, affixed or attached thereto. What this patent teaches is that when taken separately, neither of the matrix nor the membrane would retain in the stomach more than a conventional dosage form, but when the matrix is combined with the membrane, it achieves gastric retention. Tr. 653:3-25; 980:18-981:6.

WO '812 states:

> The basic concept underlying the delivery system of the present invention is the provision of a combination system, comprising at least two components, namely the matrix and the membrane affixed or attached thereto. Taken separately, neither the matrix nor the membrane would retain in the stomach more than a conventional dosage form.

DTX 229, at Gralise_JDG_00002882.

Defendant argues that WO '812 does not "teach away" from a matrix system because it does not "criticize" swellable gastric-retained dosage forms. However, "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). WO '812 would tell a POSA that "a matrix alone may not be sufficient to achieve gastric retention" and would teach away from the matrix system of the patents. Trial Tr. 979:20 – 981:10; DTX00229.

(iii) Motivation – WO '128

For the asserted '332 and '992 patent claims, Dr. Flanagan relied on WO '128 in addition to WO '107 as the primary reference in rendering his obviousness opinion. Tr. 625:9-14. As Dr. Mayersohn described, WO '128 is directed to "a new dosage form for highly water soluble medicaments, such as the antidiabetic metformin, which provides for extended release of the drug and prolonged gastric residence which enables efficient delivery of drugs normally absorbed in the upper gastrointestinal tract, and to a method for preparing such dosage form." Tr. 698:8-14; DTX 236 at GRALISE_JDG_00000057. Dr. Felton notes that "[t]he WO '128 application is focused on gastro retentive delivery system of metformin hydrochloride." Tr. 975:16-21.

As noted above, a POSA in 2001 would have had a general motivation to develop and extended release gabapentin dosage form. However, as with the WO '107 application, there are a number of factors that weigh against finding that a POSA would be motivated to combine gabapentin with the dosage form of WO '128, many of them being set forth above.

Further, while focused on metformin hydrochloride, WO '128 also contains a lengthy list of other potential drugs that may be employed in the formulation. Gabapentin is not among them, despite Neurontin's status at the time of being a blockbuster drug. According to Dr. Felton, a POSA reviewing this list would be skeptical that any or all of those drugs would be suitable in the described dosage form because there is no data for any drug other than metformin. Tr. 978-979. Furthermore, Dr. Felton points out that among the drugs listed is insulin, which cannot be absorbed orally. Tr. 979.

As noted earlier, gabapentin and metformin are not interchangeable. Tr. 983:2-8. Testimony at trial showed that there are significant difference between the two, discussed

infra. These differences along with the limited pharmacokinetic data in WO '128 are contrary to the assertion that there is a clear motivation to combine the WO '128 reference with the gabapentin IR reference to produce the inventions of the asserted claims of the '332 and '992 patents.

d. Reasonable Expectation of Success

(i) Gabapentin Patents-WO '107 in view of Rowbotham

Dr. Flanagan testified that one of ordinary skill "would have taken gabapentin and put it into one or more of Depomed's WO '107 formulations and they would have had a reasonable expectation that they would have had an efficiently absorbed gastric retained formulation." Tr. 577:5-8. Dr. Flanagan noted that while gabapentin is not one of any number of drugs mentioned in WO '107, one of skill in the art would have used that formulation for gabapentin because the reference is: (1) directed toward soluable drugs and gabapentin is a soluable drug; and (2) its directed to controlled release by diffusion and for gastric retention and for a drug that is absorbed high in the intestinal tract, and gabapentin is such a drug. Tr. at 557:9-25.

Exemplary drugs identified by WO '107 are metformin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride and ticlopidine hydrochloride. DTX 234 at GRALISE_JDG_0000844. Focusing on metformin specifically, Dr. Flanagan testified that if a POSA replaced metformin with gabapentin in WO '107, that person could reasonably expect to obtain similar release characteristics and once-daily dosing. Tr. 565:2-9. He further explained that this is because of the similarities between the two drugs: "[T]hey're both highly soluble drugs, they both have saturable transporters and they're both absorbed high in the gastrointestinal tract. So putting them into

a formulation that would maintain them in the gastric environment would insure that they don't release drug beyond their window, narrow window of absorption and when the formulation is releasing those drugs slowly, they -- the saturable transport would not be saturated and both drugs would be efficiently absorbed." Tr. 565: 11-19.

Dr. Flanagan further testified that a person of ordinary skill would have expected a therapeutic effect for the controlled release formulation as compared to the known immediate release formulation. Tr. 577:19-578:1. Effective daily doses (e.g., 300 mg to 4,800 mg) of gabapentin to treat epilepsy or neuropathic pain with an immediate release formulation were well known to those of skill in the art in October 2001. DTX 267 at GRALISE_JDG_ 00000126-28; DTX 313 at GRALISE_JDG_00000451, GRALISE_JDG_00000453-56. According to Dr. Flanagan, both 300 mg and 600 mg once-daily dose strengths would have been a natural starting points for one skilled in the art for creating a once-a-day formulation. Tr. 619:21- 620:1, 622:1-14.

However, substantial evidence was presented at trial that counters a finding of a reasonable expectation of success. For example, there are the studies conducted by Dr. Gidal and others that indicated that there was significant variability in gabapentin absorption between persons. The results of one study were published in 2000 in *Inter- and Intra-subject variability in gabapentin absorption and absolute bioavailability*, Gidal et al., Epilepsy Research 40 (2000) PTX 275 at 123-127. This states:

> The results of the present studies do highlight the point that the use of 'average' population kinetic data may be misleading in situations where substantial variability exists. In other words, although the average variability of a 600 mg oral dose of gabapentin was 49%, individual subjects may vary greatly (5-74%). The clinical implication is that 'typical' or 'usual' doses are likely to result in quite different plasma concentration in individual patients.

> Indeed, similar observations were noted by Beydoun et al. in an efficacy trial of gabapentin monotherapy.

PTX 275 at DEPOACT0970237.

Actavis's expert Dr. Mayersohn acknowledged the inter-person variability noting that the variability was three fold even after excluding "outliers." Tr. 735:1-5; 735:21 – 736:6. Dr. Gidal noted that there were several individuals who showed less bioavailability of gabapentin than that suggested by the product information, indicating that the inter-subject variability in gabapentin absorption is significant. Tr. 825:25 – 826:13. Actavis suggests that variability in gabapentin absorption would be clinically significant and points to the successful immediate release formulation of gabapentin, Neurontin. While variable absorption has not prevented the success of Neurontin, Defendant's expert Dr. Sinatra, explained that Neurontin is, in fact, ineffective in some patient, Tr. 898:22 – 899:10, which suggests that inter-person variability in gabapentin absorption does have therapeutic consequences.

Echoing many of its arguments regarding motivation, Depomed argued that a POSA would not have had a reasonable expectation of success for the following reasons:

First, gabapentin and metformin are not interchangeable;

Second, "[g]abapentin is known to be sensitive to acidic environment of the stomach and so one would not want to put a drug that degrades in acid in the stomach where it's going to reside for a number of hours;"

Third, gabapentin may not be made available in its narrow window of absorption. There is no in vivo data in the WO '107 reference showing that a dosage form would be in

fact gastrically retained or that a gabapentin containing dosage form would be gastrically retained;

Fourth, gabapentin's release rate may not avoid saturation of absorption transporters;

Fifth, food affects gabapentin absorption;

Finally, there was a lack of known correlation between gabapentin plasma concentration and therapeutic effect. Tr. 989:7 – 990:19; 990:25 – 992:24.

Further, it also appears that successfully putting gabapentin into the WO '107 dosage form would require more than routine experimentation. Dr. Felton testified as to the differences between gabapentin and metformin that would impact the ability to substitute gabapentin for metformin in the WO '107 dosage form: (i) "Metformin is a cation, so it's positively charged, not only in the body at physiological pH, but also in the low pH of the stomach. Gabapentin is a zwitterion, it has a positive charge and a negative charge." Tr. 982:23 – 983:8; 983:21 – 984:4; (ii) as mentioned earlier, gabapentin degrades into lactam; metformin does not; (iii) metformin is more than twice as soluable as gabapentin. 730:5-14; 953:8-10. These differences would impact the swelling, retention and release rates per Dr. Felton's testimony: "[T]he gastric retention mechanism, the swelling, is also related to the drug release and so adjusting the formulation to slow or increase the rate of the release could actually affect and probably would actually affect the swelling and, therefore, the gastric retention properties. ... If you change the formulation to change the release rate, because the formulation swells and that's how it achieves gastric retention, by changing the composition of the tablet, the swelling behavior could change." Tr. 984:14 – 985:9; 986:3-11.

Dr. Hopfenberg explained that metformin and gabapentin would be released differently from a dosage form. Two factors drive diffusion: (a) solubility of the drug in the swollen matrix; (b) "diffusion coefficients" or diffusivity that provides how fast the drug can move through the dosage form. As noted, gabapentin has a solubility more than two-fold less than that of metformin (135 mg/ml versus > 300 mg/ml). As Dr. Hopfenberg testified, diffusivity is related to the bulkiness of the molecule. Metformin is linear and rather small and would be more mobile than gabapentin which is a more bulky molecule with a ring structure that gives additional steric hindrance. Thus, metformin would release at a much higher rate than gabapentin. Tr. 951:21 – 952: 19.

As such, as Depomed contends, contrary to Defendant's assertions, it would not be simply a matter of routine optimization to fine-tune gabapentin in the dosage form as compared to metformin. "[T]here would be a need to adjust the formulation so that the release of the gabapentin would be at some different rate and that release could affect the swelling, and therefore, the gastric retention." 985:10-19, 986:3-11.

There is also evidence that the pharmacokinetic parameters for metformin and gabapentin would be different. Tr. 1047:6-9. Dr. Derendorf testified that gabapentin and metformin differ from each other with respect to each of the pharmacokinetic properties: absorption, distribution and elimination, such that the exposure that would result from these two products would be quite different. Tr. 1039:13-22.

With respect to absorption of the drug, as of 2001, it was known that gabapentin is taken up by transporters. However, the mechanism of absorption of metformin was unclear. Tr. 1041:8 – 1042:9; PTX 556 at 1018. Dr. Derendorf testified that if metformin and

gabapentin exhibit different absorption mechanisms, then he would not expect them to have similar pharmacokinetic behavior. Tr. 1042:10-15.

Dr. Derendorf testified that, while the precise absorption window of either drug is unknown, the absorption window of gabapentin is likely not identical to that of metformin. Tr. 1042:22 – 1043:11. Even if the absorption window were the same, Dr. Derendorf would expect there to be differences in absorption because the transporters would be different; they would have different affinity and therefore different efficiency in absorbing the drugs. Tr. 1043:12:23. Dr. Derendorf explained that one would obtain different types of absorption profiles depending on the transporter in use. The profile would depend on the affinity of the transporter for the drug and the capacity of the transporter for the drug—how much drug the transport can move into the blood stream. Tr. 1044:6-20. In 2001, the affinity and capacity of L-type amino acid transporter for gabapentin was unknown and the metformin transport mechanism was unclear. Tr. 1044:21 – 1045:2.

Looking at the pharmacokinetic property distribution, there is evidence that distribution of gabapentin and metformin is different. Metformin has a 10-fold larger volume of distribution in tissues resulting in low plasma concentration, unlike gabapentin. Tr. 1045:3-15. Dr. Derendorf explained that difference in distribution changes the pharmacokinetic profile obtained. For example, the Cmax value depends on the volume of distribution and the higher the volume of distribution, the lower the Cmax for the same amount of drug that enters the system. Tr. 1046:16-25.

With respect to the third pharmacokinetic property, elimination, Dr. Derendorf testified that although both metformin and gabapentin are eliminated by the kidneys, the mechanism of elimination is different. Whereas gabapentin is mainly eliminated by

glomerular filtration, which does not involve transporters, metformin is eliminated by tuberous secretion, which involves transporters. Metformin is therefore eliminated at a much higher rate than gabapentin. Dr. Derendorf opined that one of skill cannot expect two drugs with different eliminations to have similar pharmacokinetics. Tr. 1046:1-16. Such pharmacokinetics are contrary to a clear reasonable expectation of success on combining WO '107 with gabapentin immediate release references.

(ii) '332 and 992 patents--WO '128 in view of Rowbotham.

The WO '128 does not provide pharmacokinetic information for gabapentin, however Dr. Mayersohn testified that a person of ordinary skill in the art would have a reasonable expectation of achieving a similar effect on the pharmacokinetics of gabapentin by putting gabapentin into the WO '128 dosage form – *i.e.*, reduced C_{max}, longer T_{max} and similar $AUC_{infinity}$ compared to the immediate-release product. Tr. 705:19-706:1, 715:21-717:18, 718:16-21; 717:22-718:11. Dr. Mayersohn based his opinion with respect to this expectation of success upon the properties that both gabapentin and metformin were known to have in common, Tr. at 718:3, -- high water solubility, saturable absorption, and a limited window of absorption high in the gastrointestinal tract. Tr. 563:19-24; 5/15/2014 Tr. 698:17-20. Dr. Mayersohn opined, based on these properties, that one of ordinary skill in the art would have reasonably expected that the behavior of metformin and gabapentin would be the same when put into the WO '128 dosage form. Tr. 715:21-717:18; *see also* Tr. 626:4-628:18, 628:20-22.

However, as discussed above, a deeper look into the evidence reveals significant differences between metformin and gabapentin that undercut Dr. Mayersohn's opinion here. The evidence discussed in the prior section shows that metformin and gabapentin exhibit

substantial differences that would affect swelling, retention and release rates. Tr. 984-989. There also exists differences in solubility, pharmacokinetic properties, and they exhibit different absorption mechanism. As such, the Court cannot conclude that Actavis has met its burden to establish that there would exist a reasonable expectation of success.

e. Secondary Considerations

(i) Unmet Need

The parties have stipulated that Gralise embodies the asserted claims of the '927, '989, '756, '332 and '992 Patents. Gralise was approved in 2011 and was the first sustained release gastric retained oral dosage form for gabapentin. Tr. 679:8-11.

Experts on pain management testified for each side. Depomed's expert, Dr. Michelle Brown, who was accepted as an expert in treating neuropathic pain, testified that a long-felt need existed for a controlled release formulation of gabapentin to address the issues of compliance and minimizing side effects. Tr. 866-886. Gralise met that need. Tr. 870:1-7. Among other things, Dr. Brown also relied on her clinical experience, which includes her continuous treatment of neuropathic pain for twenty-two years, during which time she has prescribed numerous drugs, among them both immediate release and controlled release formulations of gabapentin. Tr. 867:18–868:19.

Actavis's Dr. Sinatra, while not expressly offering a contrary opinion regarding long-felt unmet need, testified that in his medical experience there are no compliance problems with taking immediate release gabapentin because, unlike medications used for treating undetectable symptoms such as high blood pressure, a patient being treated for pain would not forget to take their pain medication. Tr. 903:17-904:9. The Court overall, however, accords Dr. Sinatra's opinions less weight in light of the fact that he simply has

no experience prescribing Gralise. He testimony, based on his personal prescribing habits, is that his first choice medication for treating postherpetic neuralgia is gabapentin immediate release. Tr. 896:22-25. When asked why, he states that "it has stood the test of time", dosing is well understood, and its "a very safe drug." Tr. 897:1-10. However, he admits that Gralise is not available on the formulary at the medical centers where he practices and, therefore, he has never prescribed extended-release gabapentin. It is not unreasonable to conclude that where a physician is, for all practical purposes, unable to prescribe a certain drug, it would influence somewhat that his opinions with respect to the alternative drugs.

Thus, on balance, the weight of the evidence favors a finding of the existence of a long-felt, unmet need.

(ii) Failure of Others

Dr. Bockbrader testified that Warner-Lambert was unable to develop a controlled release dosage form of gabapentin and was skeptical of developing a controlled-release dosage form. Tr. 748:14-19. This attempt by Warner-Lambert to make a controlled release formulation of gabapentin, however, occurred at a time before it was known that gabapentin was absorbed high in the gastrointestinal tract and/or that gabapentin was absorbed through saturable transporters. Tr. 768:7-21, 770:15-771:4, 768:22-770:3.

Dr. Felton reviewed lab notebooks and related documents produced by Andrx, which tried but failed to develop an extended release form of gabapentin from 1999 to 2001. Tr. 1001:14-25, 1002:22-1005:10. Andrx's formulations, however, were not designed to be gastric retained. 1017:23-1018:10, 1019:12-1020:6. As the same formulations were also used to test delivery of Andrx's proprietary gabapentanoid prodrug

(which has a different absorption profile than gabapentin not limited to the upper gastrointestinal tract), Tr. 1019:12-1020:6, Defendant suggests that Andrx was merely using the gabapentin formulations as a baseline to compare with their proprietary gabapentanoid prodrug.

While there is some evidence that there has been failures by others to create a controlled release gabapentin formulation, the Court finds, given the findings above, this factor to be relatively neutral in the obviousness analysis.

(iii) Skepticism

Dr. Bockbrader and Dr. Gidal testified that a POSA there was skepticism as of October 2001 about the feasibility of an effective extended release gabapentin formulation. As noted above, Dr. Bockbrader testified regarding the skepticism and failure at Warner Lambert. Tr. 748:14-19 Dr. Gidal testified that, based on the unpredictable pharmacokinetics, variability in absorption, etc., discussed earlier, he was skeptical that one could craft a controlled release formulation of gabapentin that would be therapeutically effective. Tr. 816:24-817:5.

Dr. Gidal similarly also suggested XenoPort, a small biopharmaceutics firm, was skeptical of a controlled release gabapentin formulation when they decided to develop a prodrug of gabapentin, gabapentin enacarbil, that bypasses the gabapentin transporters and uses a different transporter to achieve linear, non-saturable absorption. Tr. 849:3-7, 853:12-16; PTX 269 at DEPOACT0958153; PTX 277 at DEPOACT0970277. Dr. Gidal testified, however, that he was never asked to help develop a controlled release form of gabapentin for XenoPort and that they only approached him to develop a prodrug. Tr. 860:6-15, 861:14-16.

Overall, the Court concludes that there is evidence of some skepticism in the industry, but the evidence on this factor is not especially compelling.

(iv) Commercial Success

Gralise was launched in October 2011. Since that time, Plaintiff's economics expert, Dr. Nicholson, explained that that there has been in increase in monthly prescriptions from about 3,000 in December 2011 to 23,000 in December 2013. Tr. 1069:5-16. Similarly, wholesale sales and net sales have seen corresponding increases over that time as well. Tr. 1069:20 - 1070:25.

Gralise competes in the marketplace with Neurontin, generic gabapentin, Lyrica, Horizant, Lidoderm, Cymbalta, Savella and Qutenza, which are drugs approved for PHN and related indications. PTX00703 at slide 3; Tr. 1067:2-17. The market is mature and competitive. Tr. 1068:2-14. Defendant's expert Dr. Sullivan calculated that Gralise has a very small market share of 0.24% in July 2013. Tr. 1198:19-1199:2. Market share has increase slightly year to year since 2011 (0.16% in 2012 to 0.24% in 2013), but Dr. Sullivan testified that the change was not "meaningful" and was effectively rounding error. 1198:16 - 1199:2.

Dr. Nicholson also testified about his net present value analysis, which consists of deriving the revenues and the costs and the profits through each year of a product's life. Tr. 1071-72. According to Dr. Nicholson, companies use net present value to evaluate whether to develop or invest in products. Tr. 1071. Dr. Nicholson's analysis shows that Gralise's net present value will turn positive in its 10th year on the market, which means that at that point Gralise will have recouped its R&D costs and it will have exceeded investors' required rate of return on pharmaceutical investments, and it will continue to generate

positive profits to where its NPV ultimately will be positive $34 million. Tr. 1077:8-15; 1078:8-25.

Dr. Nicholson's analysis was based on three years of actual data of Gralise sales. Tr. 1074:16-1075:15, 1099:10-13. He stated, however, in other cases he has testified in, he had 4 to 6 years of sales data on which to base his opinion. Tr. 1089:14-16. Further, Dr. Sullivan criticized the analysis, pointing to certain weaknesses. For example, he noted that Dr. Nicholson assumed that sales and marketing expenses for Gralise would be in line with an "average drug," but to date Gralise has not performed as an average drug and its sales have been far below an average drug. Tr. 1180:15-19.

Overall, based on the evidence presented at trial, the Court finds that Gralise has achieved a moderate amount of commercial success.

(v) Copying

The Court finds there is evidence of copying. To develop a generic version of the Depomed Gralise product, Actavis considered the Depomed patents and patent applications in an attempt to derive the Gralise formulation. Tr. 52:1-20. Based on the Depomed patents and applications, Actavis designed an in-house reference that included [redacted] represented Actavis' best understanding of the formulation of Gralise. Tr. 53:10-19; PTX000014 at ACTGAB000000336.

Actavis attempted to design its formulation for drug release close to the drug release in the patent and to Gralise. Tr. 57:12-15; 61:22– 62:3; PTX000014 at ACTGAB000000336. Also, Defendant [redacted] 61:14-18; PTX000014 at ACTGAB000000336.

f. Conclusion as to Whether the Gabapentin Patents Would Have Been Obvious

Defendant contends that the asserted claims of the Gabapentin Patents would have been obvious to one of ordinary skill over the WO '107 in view of an article by Michael Rowbotham along with the knowledge of a person of ordinary skill in the art. Actavis also contends that the asserted claims of the '332 and '992 Patents would have been obvious to one of ordinary skill over WO '128 and the Rowbotham article along with the knowledge of a person of ordinary skill in the art.

Approaching the question of obviousness from the perspective of a POSA as of October 2001 seeking to develop a controlled-release formulation of gabapentin, the Court finds that Actavis has failed to carry its burden of clearly demonstrating the obviousness of the Gabapentin Patents.

As an initial matter, particularly to the extent that Defendant relies on WO '107, the Court agrees with Plaintiff that Defendant's case suffers from impermissible hindsight bias. Importantly, an "invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time. The invention must be evaluated not through the eyes of the inventor, who may have been of exceptional skill, but as by one of 'ordinary skill.'" *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985). The prior art shows that although gastro-retentive drug delivery systems were an emerging art and not well developed, there were many possible approaches to a gastro-retentive drug delivery system. *See generally* Hwang reference, DTX 222. Defendant failed to establish by comparison the suitability of the WO '107 dosage form over other potential approaches. Dr. Flanagan admitted that although the *Hwang* reference taught

multiple approaches to gastric retention, he did not address any of those approaches. Tr. 661:2-7.

Additionally, the Court finds there exists evidence, detailed above, that would cast doubt on the motivation of a POSA to put gabapentin in the dosage forms of the prior art, for example food effect and degradation of gabapentin in lactam. Similarly, while there may have existed a general motivation to create a once-daily gabapentin formulation to improve compliance and possibly reduce side effects, certain unique characteristics of gabapentin, detailed above, may have dissuaded a POSA from attempting to develop an effective extended release gabapentin formulation and weigh against a finding of reasonable expectation of success.

In sum, based upon the findings set forth above, the Court finds that Defendants have not met their burden to show that the Gabapentin Patents are invalid for obviousness.

5. The '962 Patent

The '962 Patent addresses the problem of developing tablet shapes to enhance the gastric retention of swellable controlled-release oral dosage forms. Tr. 933:19 – 934:2; 505:9-12. The specification explains that, although dosage forms that swell to sizes that will prolong the residence time in the stomach, the tablet could still be expelled from the stomach depending on the tablet's orientation in the stomach. JTX 1 at col. 2. l. 52 - col. 3, l. 5. More specifically, the specification of the '962 Patent states:

> Even with swelling, a certain proportion of particles can pass through the pylorus regardless of whether the subject is in the fed mode or the fasting mode, if the particles become oriented when in the vicinity of the pylorus such that their longest dimension is in alignment with the pyloric axis. This is particularly true of tablets or caplets (cylindrical tablets with rounded ends) that are elongated in shape to facilitate swallowing. When dosage forms such as these swell due to imbibition of water, one dimension may

> achieve a length great enough to exceed the pyloric opening while the others may be significantly smaller. The dosage form will thus be retained in the stomach only if the form is oriented with the long dimension transverse to the pyloric opening. Accordingly, for a certain percentage of the administered units of these swellable forms, prolonged retention in the stomach is not achieved and the beneficial effect of the swelling is lost. There is thus only a limited assurance that the swelling will result in gastric retention of the dosage form.

Id. at col. 3, ll.1-19.

The specification explains that "by using a solid water-swellable dosage form of a particular shape, the proportion of these dosage forms that escapes through the pylorus due to a fortuitous orientation at the pylorus can be reduced or eliminated entirely while still having a dosage form that is easily swallowed." *Id.* at col. 3, ll. 23-27. The specification goes on to state in the summary of the invention that "[t]he shape that achieves this result is a non-circular and non-spherical shape which, when projected onto a planar surface, has two orthogonal axes of different lengths . . . ." *Id.* at col. 3, ll. 27-30. The patent claims two specific dosage form shapes as defined by the planar projection of the solid monolithic matrix: ". . . and wherein said matrix has a shape which when projected onto a plane, is either an oval or a parallelogram." JTX001,'962 Patent, col. 11, ll. 24-26 .

There appears to be no dispute that the priority date of the asserted claims of the '962 Patent is June 20, 2000. Def. Proposed Findings ¶ 20; Pl. Proposed Findings ¶ 1012.

a. Prior Art

The WO '107 application and *Hwang* references are discussed above.

International Publication No. WO 98/56360 ("WO '360"), referred to by Dr. Flanagan in his testimony, describes film-coated oral dosage forms for the transit of drugs, known to irritate the esophagus, to the stomach where they dissolve to release the drug.

Trial Tr. 681:18 – 682:3; Tr. 943:14-21. The dosage form of the WO '360 is designed to dissolve upon reaching the stomach to prevent direct contact of the tissues of the mouth, pharynx and esophagus with the active ingredient and to allow proper absorption of the active ingredient at the appropriate site. As relevant here, WO '360 discloses a "pharmaceutical formulation in a generally oval shape including, but not limited to, oval, modified oval and caplet-shaped form."

b. Whether the '962 Patent is Would Have Been Obvious

The '962 Patent contains 27 claims, four of which are asserted in this action against the 600 mg ANDA product. Claim 1 is the only independent claim, and recites a controlled-release dosage form for releasing a drug into at least a portion of a region defined by the stomach and upper gastrointestinal tract. The controlled-release oral dosage form recited by claim 1 consists essentially of a (1) solid monolithic matrix with drug contained therein, (2) that is non-circular in shape and has two orthogonal axes of unequal length, (3) where the matrix swells in an unrestricted manner along both axes upon imbibition of water, (4) the longer axis of the unswollen matrix does not exceed 3.0 centimeters, (5) the shorter axis of the matrix achieves a minimum length of 1.2 centimeters within one hour of immersion in water, and (6) the matrix projects the shape of an oval or parallelogram onto a plane. JTX 1 11:14-25; Tr. 934:23 – 935:20.

The remaining claims, 2-27, cover variants of the invention recited in Claim 1. JTX001 at 11:13 – 12:64. Claims 5, 8, and 10 depend upon Claim 1, while Claim 13 also depends upon Claim 10. The '962 Patent claims two specific dosage form shapes as defined by the planar projection of the solid monolithic matrix: ". . . and wherein said matrix has a

shape which when projected onto a plane, is either an oval or a parallelogram." JTX 1 col. 11 ll. 24-26.

Actavis argues that the asserted claims 5, 8, 10 and 13 would have been obvious to one of ordinary skill over the WO '107 application along with the knowledge of a person of ordinary skill in the art. As noted, all of the asserted claims depend from claim 1. Defendant's expert, Dr. Flanagan, opined that each limitation of claim 1 of the '962 patent is disclosed or suggested by WO '107. In contrast, Dr. Hopfenberg testified that WO '107 fails to teach or suggest at least two elements of Claim 1 of the '962 Patent to one of ordinary skill in the art. Tr. 944:18-22. Those two elements are (i) "wherein said matrix has a shape which when projected onto a plane, is either an oval or a parallelogram"; and (ii) "the shorter such axis achieving a minimum length of 1.2 cm within one hour of immersion of said dosage form in water." Tr. 944:18 – 945:2; JTX001 at 11:22-25.

As to the first element, it is undisputed that WO '107 does not disclose an oval-shaped or parallelogram-shaped dosage form. Tr. 633:8-15. Prior art WO '360, on the other hand, discloses an oval dosage form. DTX 235. However, WO '360 is a dosage form designed disintegrate, and does not swell, in the stomach. Tr. 942:24-25; 681:18-21. As such, the Court agrees with Plaintiff that WO '360 is of no consequence.

As to the first second, the Court again agrees with Depomed that it is not enough to say, as Dr. Flanagan testified (*see* Tr. 631:7-18) that WO '107 suggests the 1.2 centimeter limitation to one of skill in the art because of the disclosure that the WO '107 dosage forms swell to "at least twice their unswelled volume" as a means of "promot[ing] gastric retention in the fed mode." Tr. 937:16 – 938:19. Dr. Flanagan's opinion does not address the time limitation coupled to the 1.2 centimeter element of the '962 Patent inventions, *i.e.*,

"the shorter [] axis achieving a minimum length of 1.2 cm within one hour of immersion of said dosage form in water." Tr. 938:2-8.

Further, Dr. Flanagan does not point to an initial dimension of the short axis of the WO '107 dosage forms, nor to those dosage forms' rate of swelling. Tr. 630:12 – 633:7. Nor does he explain how one of skill would link (i) the disclosure that the WO '107 dosage forms swell to "at least twice" their volume, to (ii) an increase in the length of those dosage forms' shortest dimension. Tr. 630:12 – 633:7. According to Dr. Hopfenberg, a doubling of the volume of the WO '107 dosage form can only result in a doubling of its shortest linear dimension where all other orthogonal dimensions remain constant. Tr. 938:9-19. Such a circumstance would not be consistent with the unrestricted swelling required by Claim 1 of the '962 Patent. Tr. 938:15-19.

The matrices of the claimed '962 Patent dosage forms not swell in an unrestricted manner, they further swell to a specific dimension after a specific period of time. Tr. 937:16 – 938:8. The latter, additional requirement on the rate and extent of unrestricted swelling is not disclosed by WO '107. Tr. 631:9-12; 937:16 – 938:8. WO '107 does not say, for example, that its swollen dosage form achieves a minimum dimension of 1.2 centimeters after one hour of immersion as recited by Claim 1 of the '962 Patent. 631:9-12; Tr. 937:16 – 939:4.

Notably, Dr. Flanagan's opinion rests on his view that the '962 Patent inventions require administration to a fed stomach. Tr. 631:15- 21. The '962 Patent, however, does not a recite a claim element directed to gastric retention in the fed mode. Tr. 936:24-937:5. Rather, the '962 Patent specification states that "the dosage forms of the present invention

find utility when administered to subjects who are either in the fed mode or the fasting mode." JTX 1, col 7, ll. 9-11.

Contrary to Dr. Flanagan's testimony, the Court finds, based upon the testimony of Drs. Hopfenberg and Derendorf, that a POSA could not arrive at the invention of the '962 patent by routine optimization of the dosage forms disclosed in WO '107. As Dr. Hopfenberg points out, all of the elements of claim 1 not disclosed. Tr. 938:20 – 939:4 . Further, as Dr. Derendorf explained, WO '107 contains no in vivo or pharmacokinetic data demonstrating the extent to which the dosage forms are gastric retained.

Thus, for the reasons above, the Court finds that Actavis has failed to carry its burden of establishing by clear and convincing evidence that the '962 patent is invalid based upon obviousness.

G. INDEFINITENESS

Defendant argues that the asserted claims of the '280 patent are invalid because they are indefinite. Specifically, Defendant points to that part of Claim 1 which recites that the claimed dosage form must swell to a "size exceeding the pyloric diameter in the fed mode." JTX 2; Stip. Facts¶ 53. All of the other asserted claims of the '280 Patent depend from claim 1 and, therefore, are also include this limitation.

Plaintiff argues that Defendant's indefiniteness claim is not properly before the Court. Shortly before trial, Actavis filed a motion seeking to amend their invalidity contentions to add a contention that the '280 patent is invalid because it is indefinite. The Court denied that motion, finding that Actavis unreasonably delayed in bringing it and that no good cause existed to permit the amendment. As such, the Court need not reach the

issue and denies relief to Actavis to the extent it seeks a finding of invalidity of the '280 patent based on indefiniteness.

Nevertheless, had the Court been required to address the question, for the reasons below, the Court would have found that Defendant would not have met its burden to show that the '280 patent was invalid as indefinite.

1. Legal Standard

To be sufficiently definite, a patent specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2. The boundaries of the claim must be discernible to one skilled in the art based on the language of the claim, the specification, and the prosecution history, as well as that person's knowledge of the relevant field of art. *See Halliburton Energy Servs., Inc. v. M–ILLC*, 514 F.3d 1244, 1249–51 (Fed. Cir. 2008). The Supreme Court recently articulated a new standard for indefiniteness, holding that "a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments*, Inc., 134 S.Ct. 2120, 2124 (2014). The Federal Circuit has noted that "because claim construction frequently poses difficult questions over which reasonable minds may disagree, proof of indefiniteness must meet an exacting standard." *Haemonetics Corp. v. Baxter Healthcare Corp.*, 607 F.3d 776, 783 (Fed. Cir. 2010) (quotations omitted). However, "[i]f the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Exxon*,

265 F.3d at 1375. Because a patent is presumed to be valid, the evidentiary burden to show facts supporting a conclusion of invalidity for indefiniteness is one of clear and convincing evidence. *See Datamize LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1348 (Fed. Cir. 2005).

2. Analysis

As noted earlier, the pylorus is the structure in the stomach that regulates materials leaving the stomach into the intestine. Tr. 152:16-153:1. When food is in the stomach, the pylorus generally stays to prevent food from moving into the intestine before the destructive forces of the stomach have a chance to break the food down into smaller particles. Tr. 152:19-23. The pylorus will periodically open to allow some of the stomach contents to pass into the intestine, typically the smaller, broken-down particles. Tr. 235:9-19. While the reference to "pyloric diameter in the fed mode" in the '280 Patent claims does not explicitly state whether it refers to the pyloric diameter when the pylorus open or closed, in context it is clear that it is referring to the diameter when the pylorus is in an open, relaxed state.

With regard to indefiniteness, the Court first notes that 3 different courts, including this one in this case, have construed the claim language that Actavis alleges make the patent indefinite. Judge Hamilton construed it in *Depomed, Inc. v. Lupin Pharm., Inc. et al.*, No. C-09-05587 PJH (N.D. Cal. 2011) and Judge Breyer construed it in *Depomed, Inc. v. Ivax Corp.*, No. C-06-00100 CRB (N.D. Cal. 2006). This would indicate that the patent does not fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

Furthermore, guidance can be found in the specification. One of skill in the art reads the following passage from the '280 Patent specification for guidance as to the particle size that promotes retention in the fed stomach: "Indigestible particles greater than the size of the pylorus are retropelled and retained in the stomach. Particles exceeding about 1 cm in size are thus retained in the stomach for approximately 4 to 6 hours. The dosage form of the present invention is designed to achieve the minimal size through swelling following ingestion during the fed mode." '280 Patent, JTX002, col. 11, l. 66 to col. 12, l. 5. Thus, this statement indicates that (i) indigestible particles "greater than the size of the pylorus" that "exceed[] about 1 cm in size" are retained in the stomach, and by extension (ii) the swellable dosage forms claimed in the '280 Patent are intended to obtain this "minimal size . . . following ingestion during the fed mode."

Extrinsic evidence provides guidance as well. According to Dr. Annunziata, the overall diameter of the human pylorus during the fed state for the brief time periods it is open is approximately one centimeter. Tr. 245:25 – 246:16. Also, one study, taking into account the broader variability between individuals, reported the average diameter of the resting human pylorus as 12.8 ± 0.7 millimeters. Tr. 244:16-19, 259:15-25; PTX000245 at DEPOACT0114761.

Consequently, based on the above, the Court does not find the '280 patent to be invalid as it does not "fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus*, 134 S.Ct. at 2120.

H. CONCLUSION

For the reasons above, the Court finds in favor of Plaintiff on all claims in this case. An appropriate judgment accompanies this Opinion.

/s/ JOEL A. PISANO
United States District Judge

Dated: August 18, 2014